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(54) **Metalloprotease inhibitors**

Metalloproteinase-Inhibitoren

Inhibiteurs de la métalloprotéinase

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Description

[0001] This invention relates to a series of substituted α-aminosulphonyl-acetohydroxamic acids which are inhibitors of zinc-dependent metalloprotease enzymes. In particular, the compounds are inhibitors of certain members of the matrix metalloprotease (MMP) family.

[0002] Matrix metalloproteases (MMPs) constitute a family of structurally similar zinc-containing metalloproteases, which are involved in the remodelling and degradation of extracellular matrix proteins, both as part of normal physiological processes and in pathological conditions. Since they have high destructive potential, MMPs are usually under close regulation and failure to maintain MMP regulation has been implicated as a component of a number of diseases and conditions including pathological conditions, such as atherosclerotic plaque rupture, heart failure, restenosis, periodontal disease, tissue ulceration, wound repair, cancer metastasis, tumour angiogenesis, age-related macular degeneration, fibrotic disease, rheumatoid arthritis, osteoarthritis and inflammatory diseases dependent on migratory inflammatory cells.

[0003] Another important function of certain MMPs is to activate various enzymes, including other MMPs, by cleaving the pro-domains from their protease domains. Thus some MMPs act to regulate the activities of other MMPs, so that over-production of one MMP may lead to excessive proteolysis of extracellular matrix by another. Moreover, MMPs have different substrate preferences (shown in the following Table for selected family members) and different functions within normal and pathological conditions. For recent reviews of MMPs, see Current Pharmaceutical Design, 1996, 2, 624 and Exp. Opin. Ther. Patents, 1996, 6, 1305.

TABLE

Enzyme	Other Names	Preferred Substrates
MMP-1	collagenase-1; interstitial collagenase	collagens I, II, III, VII, X; gelatins
MMP-2	gelatinase A; 72kDa gelatinase	gelatins; collagens IV, V, VII, X; elastin; fibronectin; activates pro-MMP-13
MMP-3	stromelysin-1	proteoglycans; laminin; fibronectin; gelatins
MMP-8	collagenase-2; neutrophil collagenase	collagens I, II, III
MMP-9	gelatinase B; 92kDa gelatinase	gelatins; collagens IV, V; elastin
MMP-13	collagenase-3	collagens I, II, III; gelatins
MMP-14	MT-MMP-1	activates pro-MMP-2 & 13; gelatins

[0004] Excessive production of MMP-3 is thought to be responsible for pathological tissue breakdown which underlies a number of diseases and conditions. For example, MMP-3 has been found in the synovium and cartilage of osteoarthritis and rheumatoid arthritis patients, thus implicating MMP-3 in the joint damage caused by these diseases: see Biochemistry, 1989, 28, 8691 and Biochem. J., 1989, 258, 115. MMP-13 is also thought to play an important role in the pathology of osteoarthritis and rheumatoid arthritis: see Lab. Invest., 1997, 76, 717 and Arthritis Rheum., 1997, 40, 1391. The compounds of the present invention inhibit both MMP-3 and MMP-13 and thus may be of utility in treating these diseases.

[0005] The over-expression of MMP-3 has also been implicated in the tissue damage and chronicity of chronic wounds, such as venous ulcers, diabetic ulcers and pressure sores: see Brit. J. Dermatology, 1996, 135, 52.

[0006] Furthermore, the production of MMP-3 may also cause tissue damage in conditions where there is ulceration of the colon (as in ulcerative colitis and Crohn's disease: see J. Immunol., 1997 158, 1582 and J. Clin. Pathol., 1994, 47, 113) or of the duodenum (see Am. J. Pathol., 1996, 148, 519).

[0007] Moreover, MMP-3 is also thought to be involved in skin diseases such as dystrophic epidermolysis bullosa (see Arch. Dermatol. Res., 1995, 287, 428) and dermatitis herpetiformis (see J. Invest. Dermatology, 1995, 105, 184).

[0008] Rupture of atherosclerotic plaques by MMP-3 has also been described (see e.g. Circulation, 1997, 96, 396). Thus, MMP-3 inhibitors may find utility in the treatment of conditions caused by or complicated by embolic phenomena such as cardiac or cerebral infarctions.

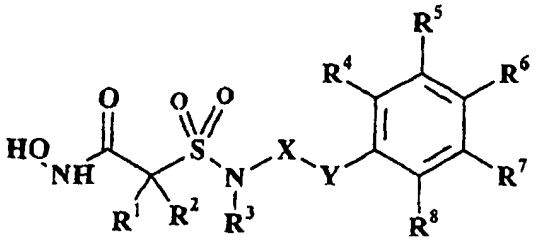
[0009] Studies of human cancers have shown that MMP-2 is activated on the invasive tumour cell surface (see J. Biol.Chem., 1993, 268, 14033) and BB-94, a non-selective peptidic hydroxamate MMP inhibitor, has been reported to decrease the tumour burden and prolong the survival of mice carrying human ovarian carcinoma xenografts (see Cancer Res., 1993, 53, 2087). Certain compounds of the present invention inhibit MMP-2 and therefore may be useful in the treatment of cancer metastasis and tumour angiogenesis.

[0010] Various series of MMP inhibitors have appeared in the literature which have a carbonyl moiety (CO) and a

sulphone moiety (SO_2) with a two atom "spacer" interposed between them. For example, α-arylsulphonamido-substituted acetohydroxamic acids are disclosed in EP-A-0606046, WO-A-9627583 and WO-A-9719068, whilst EP-A-0780386 discloses certain related sulphone-substituted hydroxamic acids.

[0011] The compounds of the present invention represent a new class of compounds, and are inhibitors of some of the members of the MMP family. In particular, they are potent inhibitors of MMP-3 and MMP-13, with certain compounds exhibiting varying degrees of selectivity over other MMPs, such as MMP-1, MMP-2 and MMP-9. Certain of the compounds are potent MMP-2 inhibitors.

[0012] Thus, according to one aspect of the present invention, there is provided a compound of formula (I):



(I)

and a pharmaceutically- and/or veterinarily-acceptable salt thereof, and a solvate of such compound and salt, wherein

R^1 and R^2 are each independently H,
C_{2-6} alkenyl, aryl(C_{1-6} alkyl), heteroaryl(C_{1-6} alkyl), aryloxy(C_{1-6} alkyl), heteroaryloxy(C_{1-6} alkyl),
C_{1-6} alkyl optionally substituted by NH_2, C_{2-6} acylamino, OH, or by CO_2H,
or R^1 and R^2 can be taken together with the carbon atom to which they are attached, to form a 4- to 8-membered saturated carbocyclic or heterocyclic ring, which heterocyclic ring has 1 or 2 hetero-groups selected from O, $S(O)_n$ or NR^9 in the ring,
R^3 is H, C_{1-6} alkyl or (C_{1-6} alkoxy)C_{1-6} alkyl,
R^4, R^5, R^7 and R^8 are each independently H, C_{1-6} alkyl, C_{1-6} alkoxy, CN or halogen,
R^6 is H, aryl, heteroaryl, aryloxy or heteroaryloxy, C_{1-6} alkyl, C_{1-6} alkoxy, CN or halogen,
R^9 is H or C_{1-6} alkyl,
n is 0,1 or 2,
X is C_{1-6} alkylene or C_{2-6} alkenylene,
Y is a direct link, CH=CH or O,

wherein "aryl" is phenyl optionally fused with another ring selected from furan, dioxolan, and pyran,
which group is optionally mono- or disubstituted by substituents independently seleceted from halogen, CN, C_{1-6} alkyl optionally substituted by OH or NH_2, C_{1-6} alkoxy, perfluoro(C_{1-6} alkyl) and perfluoro(C_{1-6} alkoxy),
and wherein "heteroaryl" is a 5- or 6-membered aromatic heterocycle with one or two heteroatoms in the ring, which heteroatoms are independently selected from O, N and S, which heteroaryl is optionally mono- or disubstituted by substituents independently selected from halogen, CN, C_{1-6} alkyl optionally substituted by OH or NH_2, C_{1-6} alkoxy, perfluoro(C_{1-6} alkyl) and perfluoro(C_{1-6} alkoxy).

[0013] In the above definition, unless otherwise indicated, alkyl, alkenyl, alkylene and alkenylene groups having three or more carbon atoms may be straight chain or branched chain.

[0014] The compounds of formula (I) may contain one or more chiral centres and therefore can exist as stereoisomers, i.e. as enantiomers or diastereoisomers, as well as mixtures thereof. The invention includes both the individual stereoisomers of the compounds of formula (I) and any mixture thereof. Separation of diastereoisomers may be achieved by conventional techniques, e.g. by fractional crystallisation or chromatography (including HPLC) of a diastereoisomeric mixture of a compound of formula (I) or a suitable salt or derivative thereof. An individual enantiomer of a compound of formula (I) may be prepared from a corresponding optically pure intermediate or by resolution, either by HPLC of the racemate using a suitable chiral support or, where appropriate, by fractional crystallisation of the diastereoisomeric salts formed by reaction of the racemate with a suitable optically active base or acid, as appropriate to the specific compound to be resolved. Furthermore, compound of formula (I) which contain alkenyl groups can exist as *cis*- or

trans- geometric isomers. Again, the invention includes both the separated individual geometric isomers as well as mixtures thereof.

[0015] Also included in the invention are radiolabelled derivatives of compounds of formula (I) which are suitable for biological studies.

[0016] The pharmaceutically acceptable salts of the compounds of the formula (I) include the acid addition and the base salts thereof.

[0017] Suitable acid addition salts are formed from acids which form non-toxic salts and examples are the hydrochloride, hydrobromide, hydroiodide, sulphate, hydrogen sulphate, nitrate, phosphate, hydrogen phosphate, acetate, maleate, fumarate, lactate, tartrate, citrate, gluconate, succinate, benzoate, methanesulphonate, benzenesulphonate and p-toluenesulphonate salts.

[0018] Suitable base salts are formed from bases which form non-toxic salts and examples are the aluminium, calcium, lithium, magnesium, potassium, sodium, zinc and diethanolamine salts.

[0019] For a review on suitable salts see Berge et al, J. Pharm. Sci., 66, 1-19 (1977).

[0020] Preferably R^1 is H.

[0021] Preferably R^2 is H.

[0022] Preferably R^3 is H or C_{1-6} alkyl.

More preferably R^3 is H or CH_3.

[0023] Preferably R^4 is H.

[0024] Preferably R^5 is H or C_{1-6} alkyl.

More preferably $R^5$is H or CH_3.

[0025] Preferably R^6 is H, aryl^1 or aryl^{1}oxy wherein "aryl^1" is phenyl optionally mono- or disubstituted by substituents selected from halogen and CN.

More preferably R^6 is H, aryl^2 or aryl^{2}oxy wherein "aryl^2" is phenyl optionally 4-substituted by substituents selected from Cl and CN.

Most preferably R^6 is H, phenyl, phenoxy, 4-cyanophenyl or 4-chlorophenyl.

[0026] Preferably R^7 is H.

[0027] Preferably R^8 is H.

[0028] Preferably X is CH_2, $(CH_2)_2$, $(CH_2)_3$, or is $CH_2CH{=}CH$ wherein the terminal methinyl carbon of this group is linked to the Y moiety.

[0029] A preferred group of compounds, salts and solvates is that in which at least two of the groups R^4, R^5, R^7 and R^8 are all H.

[0030] Another preferred group of compounds, salts and solvates is that in which R^4, R^7 and R^8 are all H and R^5 is CH_3.

[0031] Yet another preferred group of compounds, salts and solvates is that in which R^1, R^2, R^4, R^7 and R^8 are all H,

R^3 is H or CH_3,
$R^5$is H or CH_3,
R^6 is H, phenyl, phenoxy, 4-cyanophenyl or 4-chlorophenyl,
X is CH_2, $(CH_2)_2$, $(CH_2)_3$, or $CH_2CH{=}CH$,

and the salts and solvates thereof.

[0032] The most preferred compounds, salts and solvates are those of the Examples and the salts and solvates thereof.

[0033] The invention further provides synthetic methods for the production of compounds, salts and solvates of the invention, which are described below and in the Examples. The skilled man will appreciate that the compounds, salts and solvates of the invention could be made by methods other than those herein described, by adaptation of the methods herein described and/or adaptation of methods known in the art, for example the art described herein.

[0034] In the Methods below, unless otherwise specified, the substituents are as defined above with reference to the compounds of formula (I).

[0035] Where desired or necessary, the compound of formula (I) can be converted into a pharmaceutically or veterinarily acceptable salt thereof, conveniently by mixing together solutions of a compound of formula (I) and the desired acid or base, as appropriate. The salt may be precipitated from solution and collected by filtration, or may be collected by other means such as by evaporation of the solvent. In some cases, the salt may be the direct product of a reaction to make a compound or salt of the invention in a solvent, in which case no further transformation step would be necessary.

[0036] Where desired or necessary, solvates of the compounds and salts of the invention may be made by standard methods well known in the art. In some cases, the solvate may be the direct product of a reaction to make a compound or salt of the invention, in which case no further transformation step would be necessary.

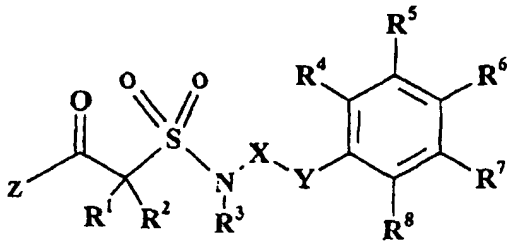
[0037] It is to be understood that the synthetic transformation methods mentioned herein may be carried out in various different sequences in order that the desired compounds can be efficiently assembled. The skilled chemist will exercise his judgement and skill as to the most efficient sequence of reactions for synthesis of a given target compound.

[0038] It will be apparent to those skilled in the art that sensitive functional groups may need to be protected and deprotected during synthesis of a compound of the invention. This may be achieved by conventional methods, for example as described in "Protective Groups in Organic Synthesis" by TW Greene and PGM Wuts, John Wiley & Sons Inc (1991).

[0039] The following processes are illustrative of the general synthetic procedures which may be adopted in order to obtain the compounds of the invention.

[0040] Unless otherwise stated, the substituents of the intermediates described below are as defined above for formula (I).

[0041] A compound of formula (I) may be prepared directly from an acid derivative of formula (II):



(II)

where Z is chloro, bromo, iodo, C_{1-3} alkyloxy or HO.

[0042] When prepared directly from the ester of formula (II), where Z is C_{1-3} alkyloxy, the reaction may be carried out by treatment of the ester with hydroxylamine, preferably up to a 3-fold excess of hydroxylamine, in a suitable solvent at from room temperature to 85°C. The hydroxylamine is conveniently generated in situ from a suitable salt such as its hydrochloride salt by conducting the reaction in the presence of a suitable base such as an alkali metal carbonate or bicarbonate, e.g. potassium carbonate. Preferably the solvent is a mixture of methanol and tetrahydrofuran and the reaction is temperature is from 65 to 70°C.

[0043] Alternatively, the ester (II, where Z is C_{1-3} alkyloxy) may be converted by conventional hydrolysis to the corresponding carboxylic acid (II, Z is HO) which is then transformed to the required hydroxamic acid of formula (I).

[0044] Preferably the hydrolysis of the ester is effected under basic conditions using up to a 6-fold excess of an alkali metal hydroxide in aqueous solution, optionally in the presence of a co-solvent, at from about room temperature to 85°C. Typically the co-solvent is a mixture of methanol and tetrahydrofuran or a mixture of methanol and 1,4-dioxan and the reaction temperature is from 40 to about 70°C.

[0045] The subsequent coupling step may be achieved using conventional amide-bond forming techniques, e.g. via the acyl halide derivative (II, Z is Cl, I or Br) and hydroxylamine hydrochloride in the presence of an excess of a tertiary amine such as triethylamine or pyridine to act as acid-scavenger, optionally in the presence of a catalyst such as 4-dimethylaminopyridine, in a suitable solvent such as dichloromethane, at from about 0°C to about room temperature. For convenience, pyridine may also be used as the solvent.

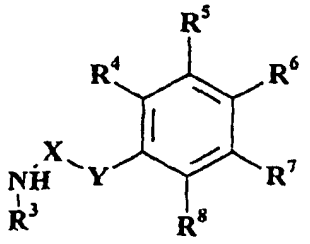
[0046] In particular, any one of a host of amino acid coupling variations may be used. For example, the acid of formula (II) wherein Z is HO may be activated using a carbodiimide such as 1,3-dicyclohexylcarbodiimide or 1-ethyl-3-(3-dimethylaminoprop-1-yl)carbodiimide optionally in the presence of 1-hydroxybenzotriazole and/or a catalyst such as 4-dimethylaminopyridine, or by using a halotrisaminophosphonium salt such as bromotris(pyrrolidino)-phosphonium hexafluorophosphate. Either type of coupling is conducted in a suitable solvent such as dichloromethane or dimethylformamide, optionally in the presence of a tertiary amine such as N-methylmorpholine or N-ethyldiisopropylamine (for example when either the hydroxylamine or the activating reagent is presented in the form of an acid addition salt), at from 0°C to room temperature. Typically, from 1.1 to 2.0 molecular equivalents of the activating reagent and from 1.0 to 4.0 molecular equivalents of any tertiary amine present are employed.

[0047] A preferred reagent for mediating the coupling reaction is O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU).

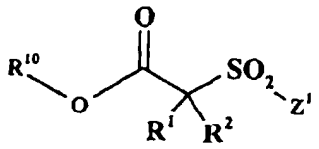
[0048] Preferably a solution of the acid (II, Z is HO) and N-ethyldiisopropylamine in a suitable solvent such as anhydrous dimethylformamide or anhydrous 1-methylpyrrolidin-2-one, under nitrogen, is treated with up to a 1.5-fold excess of HATU at room temperature followed, after 15 to 30 minutes, with up to about a 3-fold excess of hydroxylamine

hydrochloride and up to about a 4-fold excess of N-ethyldiisopropylamine, optionally in the same solvent, at the same temperature.

[0049] An ester of formula (II, Z is C_{1-3} alkyloxy) may be prepared from an amine of formula (III) by sulphonylation with a compound of formula (IV), wherein R^{10} is C_{1-3} alkyloxy and Z^1 is a leaving group such as Br, I or Cl.



(III)



(IV)

Preferably, Z^1 is chloro.

[0050] The reaction may be effected in the presence of an appropriate base in a suitable solvent at from 0°C to room temperature. For example, when both R^1 and R^2 are hydrogen, an appropriate base is 1,8-diazabicyclo[5.4.0]undec-7-ene and a suitable solvent is dichloromethane.

[0051] Certain esters of formula (II, Z is C_{1-3} alkyloxy) wherein at least one of R^1 and R^2 is other than hydrogen may be conveniently obtained from the α-carbanion of an ester of formula (II) wherein at least one of R^1 and R^2 is hydrogen by conventional C-alkylation procedures using an alkylating agent of formula (VA) or (VB):

$$RZ^2 \qquad (VA)$$

$$Z^2(CH_2)_qZ^3 \qquad (VB)$$

wherein R is as previously defined for R^1 or R^2 but is not hydrogen, Z^2 and Z^3 may be the same or different and are suitable leaving groups such as chloro, bromo, iodo, C_1-C_4 alkanesulphonyloxy, trifluoromethanesulphonyloxy or arylsulphonyloxy (e.g. benzenesulphonyloxy or p-toluenesulphonyloxy), and q is 3, 4, 5, 6 or 7.

[0052] Preferably, Z^2 and Z^3 are selected from bromo, iodo and p-toluenesulphonyloxy.

[0053] The carbanion may be generated using an appropriate base in a suitable solvent. Typical base-solvent combinations may be selected from lithium, sodium or potassium hydride, lithium, sodium or potassium bis(trimethylsilyl) amide, lithium diisopropylamide and butyllithium, together with toluene, ether, 1,2-dimethoxyethane, tetrahydrofuran, 1,4-dioxan, dimethylformamide, N,N-dimethylacetamide, 1-methylpyrrolidin-2-one and any mixture thereof.

[0054] Preferably the base is sodium hydride and the solvent is dimethylformamide, optionally with tetrahydrofuran as co-solvent, or 1-methylpyrrolidin-2-one. For monoalkylation up to a 10% excess of base is employed whilst, for dialkylation, from 2 to 3 molar equivalents are generally appropriate.

[0055] Typically, the carbanion is generated at about room temperature, under nitrogen, and subsequently treated with the required alkylating agent at the same temperature. Clearly, when dialkylation is required and R^1 and R^2 are different, the substituents may be introduced in tandem in a "one-pot reaction" or in separate steps.

[0056] An amine of formula (III) may be obtained by standard chemical procedures. Other amines of formula (III), when neither commercially available nor subsequently described, can be obtained either by analogy with the processes described in the Preparations section below or by conventional synthetic procedures, in accordance with standard textbooks on organic chemistry or literature precedent, from readily accessible starting materials using appropriate reagents and reaction conditions.

[0057] Moreover, persons skilled in the art will be aware of variations of, and alternatives to, those processes described hereinafter in the Examples and Preparations sections which allow the compounds defined by formula (I) to be obtained.

[0058] The biological activities of the compounds of the present invention were determined by the following test methods, which are based on the ability of the compounds to inhibit the cleavage of various fluorogenic peptides by MMPs 1, 2, 3, 9, 13 and 14.

[0059] The assays for MMPs 2, 3, 9 and 14 are based upon the original protocol described in fed.Euro.Biochem.

Soc., 1992, 296, 263, with the minor modifications described below.

Inhibition of MMP-1

Enzyme Preparation

[0060] Catalytic domain MMP-1 was prepared in Pfizer Central Research laboratories. A stock solution of MMP-1 (1μM) was activiated by the addition of aminophenylmercuric acetate (APMA), at a final concentration of 1mM, for 20 minutes at 37°C. MMP-1 was then diluted in Tris-HCl assay buffer (50mM Tris, 200mM NaCl, 5mM $CaCl_2$, 20μM $ZnSO_4$ and 0.05% Brij 35, pH 7.5) to a concentration of 10nM. The final concentration of enzyme used in the assay was 1nM.

Substrate

[0061] The fluorogenic substrate used in this assay was Dnp-Pro-β-cyclohexyl-Ala-Gly-Cys(Me)-His-Ala-Lys-(N-Me-Ala)-NH_2 as originally described in Anal. Biochem., 1993, 212, 58. The final substrate concentration used in the assay was 10μM.

Determination of Enzyme Inhibition

[0062] The test compound was dissolved in dimethyl sulphoxide and diluted with assay buffer so that no more than 1% dimethyl sulphoxide was present. Test compound and enzyme were added to each well of a 96 well plate and allowed to equilibrate for 15 minutes at 37°C in an orbital shaker prior to the addition of substrate. Plates were then incubated for 1 hour at 37°C prior to determination of fluorescence (substrate cleavage) using a fluorimeter (Fluostar; BMG LabTechnologies, Aylesbury, UK) at an excitation wavelength of 355 nm and emission wavelength of 440 nm. The potency of inhibition was measured from the amount of substrate cleavage obtained using a range of test compound concentrations and, from the resulting dose-response curve, an IC_{50} value (the concentration of inhibitor required to inhibit 50% of the enzyme activity) was calculated.

Inhibition of MMP-2, MMP-3 and MMP-9

Enzyme Preparation

[0063] Catalytic domains MMP-2, MMP-3 and MMP-9 were prepared in Pfizer Central Research laboratories. A stock solution of MMP-2, MMP-3 or MMP-9 (1μM) was activated by the addition of APMA. For MMP-2 and MMP-9, a final concentration of 1mM APMA was added, followed by incubation for 1 hour at 37°C. MMP-3 was activated by the addition of 2mM APMA, followed by incubation for 3 hours at 37°C. The enzymes were then diluted in Tris-HCl assay buffer (100mM Tris, 100mM NaCl, 10mM $CaCl_2$ and 0.16% Brij 35, pH 7.5) to a concentration of 10nM. The final concentration of enzyme used in the assays was 1nM.

Substrate

[0064] The fluorogenic substrate used in this screen was Mca-Arg-Pro-Lys-Pro-Tyr-Ala-Nva-Trp-Met-Lys(Dnp)-NH_2 (Bachem Ltd., Essex, UK) as originally described in J.Biol.Chem., 1994, 269, 20952. This substrate was selected because it has a balanced hydrolysis rate against MMPs 2, 3 and 9 (k_{cat}/k_m of 54,000, 59,400 and 55,300 s^{-1} M^{-1} respectively). The final substrate concentration used in the assay was 5μM.

Determination of Enzyme Inhibition

[0065] The test compound was dissolved in dimethyl sulphoxide and diluted with assay buffer so that no more than 1% dimethyl sulphoxide was present. Test compound and enzyme were added to each well of a 96 well plate and allowed to equilibrate for 15 minutes at 37°C in an orbital shaker prior to the addition of substrate. Plates were then incubated for 1 hour at 37°C, prior to determination of fluorescence using a fluorimeter (Fluostar; BMG LabTechnologies, Aylesbury, UK) at an excitation wavelength of 328nm and emission wavelength of 393nm. The potency of inhibition was measured from the amount of substrate cleavage obtained using a range of test compound concentrations and, from the resulting dose-response curve, an IC_{50} value (the concentration of inhibitor required to inhibit 50% of the enzyme activity) was calculated.

Inhibition of MMP- 13

Enzyme Preparation

[0066] Human recombinant MMP-13 was prepared by PanVera Corporation (Madison, Wisconsin) and characterised at Pfizer Central Research laboratories. A 1.9 mg/ml stock solution was activated with 2mM APMA for 2 hours at 37°C. MMP-13 was then diluted in assay buffer (50mM Tris, 200mM NaCl, 5mM $CaCl_2$, 20μM $ZnCl_2$ and 0.02% Brij 35, pH 7.5) to a concentration of 5.3nM. The final concentration of enzyme used in the assay was 1.3nM.

Substrate

[0067] The fluorogenic substrate used in this screen was Dnp-Pro-Cha-Gly-Cys(Me)-His-Ala-Lys(NMA)-NH_2. The final substrate concentration used in the assay was 10μM.

Determination of Enzyme Inhibition

[0068] The test compound was dissolved in dimethyl sulphoxide and diluted with assay buffer so that no more than 1% dimethyl sulphoxide was present. Test compound and enzyme were added to each well of a 96 well plate. The addition of substrate to each well initiated the reaction. Fluorescence intensity was determined using a 96 well plate fluorimeter (Cytofluor II; PerSeptive Biosystems, Inc., Framingham, MA) at an excitation wavelength of 360nm and emission wavelength of 460nm. The potency of inhibition was measured from the amount of substrate cleavage obtained using a range of test compound concentrations and, from the resulting dose-response curve, an IC_{50} value (the concentration of inhibitor required to inhibit 50% of the enzyme activity) was calculated.

Inhibition of MMP-14

Enzyme Preparation

[0069] Catalytic domain MMP-14 was prepared in Pfizer Central Research laboratories. A 10μM enzyme stock solution was activated for 20 minutes at 25°C following the addition of 5μg/ml of trypsin (Sigma, Dorset, UK). The trypsin activity was then neutralised by the addition of 50μg/ml of soyabean trypsin inhibitor (Sigma, Dorset, UK), prior to dilution of this enzyme stock solution in Tris-HCl assay buffer (100mM Tris, 100nM NaCl, 10mM $CaCl_2$, 0.16% Brij 35, pH 7.5) to a concentration of 10nM. The final concentration of enzyme used in the assay was 1nM.

Substrate

[0070] The fluorogenic substrate used in this screen was Mca-Pro-Leu-Gly-Leu-Dpa-Ala-Arg-NH_2 (Bachem Ltd., Essex, UK) as described in J.Biol.Chem., 1996, 271, 17119.

Determination of enzyme inhibition

[0071] This was performed as described for MMPs 2, 3 and 9.

[0072] For use in mammals, including humans, the compounds of formula (I) or their salts or solvates of such compounds or salts, can be administered alone, but will generally be administered in admixture with a pharmaceutically or veterinarily acceptable diluent or carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example, they can be administered orally, including sublingually, in the form of tablets containing such excipients as starch or lactose, or in capsules or ovules either alone or in admixture with excipients, or in the form of elixirs, solutions or suspensions containing flavouring or colouring agents. The compound or salt could be incorporated into capsules or tablets for targetting the colon or duodenum via delayed dissolution of said capsules or tablets for a particular time following oral administration. Dissolution could be controlled by susceptibility of the formulation to bacteria found in the dudodenum or colon, so that no substantial dissolution takes places before reaching the target area of the gastrointestinal tract. The compounds or salts can be injected parenterally, for example, intravenously, intramuscularly or subcutaneously. For parenteral administration, they are best used in the form of a sterile aqueous solution or suspension which may contain other substances, for example, enough salt or glucose to make the solution isotonic with blood. They can be administered topically, in the form of sterile creams, gels, suspensions, lotions, ointments, dusting powders, sprays, drug-incorporated dressings or via a skin patch. For example they can be incorporated into a cream consisting of an aqueous or oily emulsion of polyethylene glycols or liquid paraffin, or they can be incorporated into an ointment consisting of a white wax soft paraffin base, or as hydrogel with cellulose or

polyacrylate derivatives or other viscosity modifiers, or as a dry powder or liquid spray or aerosol with butane/propane, HFA or CFC propellants, or as a drug-incorporated dressing either as a tulle dressing, with white soft paraffin or polyethylene glycols impregnated gauze dressings or with hydrogel, hydrocolloid, alginate or film dressings. The compound or salt could also be administered intraocularly as an eye drop with appropriate buffers, viscosity modifiers (e.g. cellulose derivatives), preservatives (e.g. benzalkonium chloride (BZK)) and agents to adjust tenicity (e.g. sodium chloride). Such formulation techniques are well-known in the art.

[0073] For veterinary use, a compound of formula (I), or a veterinarily acceptable salt thereof, or a veterinarily acceptable solvate of either entity, is administered as a suitably acceptable formulation in accordance with normal veterinary practice and the veterinary surgeon will determine the dosing regimen and route of administration which will be most appropriate for a particular animal.

[0074] All such formulations may also contain appropriate stabilisers and preservatives.

[0075] Reference to treatment includes prophylaxis as well as alleviation of established conditions, or the symptoms thereof.

[0076] For oral and parenteral administration to animal (inc. human) patients, the daily dosage level of the compounds of formula (I) or their salts will be from 0.001 to 20, preferably from 0.01 to 20, more preferably from 0.1 to 10, and most preferably from 0.5 to 5 mg/kg (in single or divided doses). Thus tablets or capsules of the compounds will contain from 0.1 to 500, preferably from 50 to 200, mg of active compound for administration singly or two or more at a time as appropriate.

[0077] For topical administration to animal (inc. human) patients with chronic wounds, the daily dosage level of the compounds, in suspension or other formulation, could be from 0.00001 to 1mg/ml, preferably from 0.001 to 0.1 mg/ml.

[0078] The physician or veterinary surgeon in any event will determine the actual dosage which will be most suitable for a an individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case; there can of course be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

[0079] Thus the invention provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate of either entity, together with a pharmaceutically acceptable diluent or carrier.

[0080] It further provides a veterinary formulation comprising a compound of formula (I), or a veterinarily acceptable salt thereof, or a veterinarily acceptable solvate of either entity, together with a veterinarily acceptable diluent or carrier.

[0081] The invention also provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate of either entity, or a pharmaceutical composition containing any of the foregoing, for use as a human medicament.

[0082] In addition, it provides a compound of formula (I), or a veterinarily acceptable salt thereof, or a veterinarily acceptable solvate of either entity, or a veterinary formulation containing any of the foregoing, for use as a medicament for non-human animal.

[0083] In yet another aspect, the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate of either entity, for the manufacture of a human medicament for the treatment of a condition mediated by one or more MMPs.

[0084] It also provides the use of a compound of formula (I), or a veterinarily acceptable salt thereof, or a veterinarily acceptable solvate of either entity, for the manufacture of an animal medicament for the treatment of a condition mediated by one or more MMPs.

[0085] Moreover, the invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, or a pharmaceutically acceptable solvate of either entity, for the manufacture of a human medicament for the treatment of atherosclerotic plaque rupture, myocardial infarction, heart failure, restenosis, stroke, periodontal disease, tissue ulceration, wound repair, skin diseases, cancer metastasis, tumour angiogenesis, age-related macular degeneration, fibrotic disease, rheumatoid arthritis, osteoarthritis and inflammatory diseases dependent on migratory inflammatory cells.

[0086] It also provides the use of a compound of formula (I), or a veterinarily acceptable salt thereof, or a veterinarily acceptable solvate containing either entity, for the manufacture of an animal medicament for the treatment of atherosclerotic plaque rupture, myocardial infarction, heart failure, restenosis, stroke, periodontal disease, tissue ulceration, wound repair, skin diseases, cancer metastasis, tumour angiogenesis, age-related macular degeneration, fibrotic disease, rheumatoid arthritis, osteoarthritis and inflammatory diseases dependent on migratory inflammatory cells.

[0087] The syntheses of the compounds of the invention and of the intermediates for use therein are illustrated by the following Examples and Preparations.

EXAMPLES AND PREPARATIONS

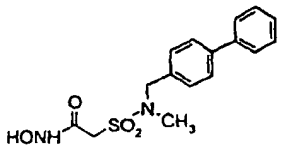
[0088] Room temperature means 20 to 25°C. Flash chromatography refers to column chromatography on silica gel

(Kieselgel 60, 230-400 mesh). Melting points are uncorrected. ^{1}H Nuclear magnetic resonance (NMR) spectra were recorded using a Bruker AC300, a Varian Unity Inova-300 or a Varian Unity Inova-400 spectrometer and were in all cases consistent with the proposed structures. Characteristic chemical shifts are given in parts-per-million downfield from tetramethylsilane using conventional abbreviations for designation of major peaks: e.g. s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Mass spectra were recorded using a Finnigan Mat. TSQ 7000 or a Fisons Intruments Trio 1000 mass spectrometer. LRMS means low resolution mass spectrum and the calculated and observed ions quoted refer to the isotopic composition of lowest mass. Hexane refers to a mixture of hexanes (hplc grade) b.p. 65-70°C. Ether refers to diethyl ether. Acetic acid refers to glacial acetic acid. 1-Hydroxy-7-aza-1H-1,2,3-benzotriazole (HOAt), *N*-[(dimethylamino)-1H-1,2,3-triazolo[4,5-*b*]pyridin-1-ylmethylene)-*N*-methylmethaninium hexafluorophosphate *N*-oxide (HATU) and 7-azabenzotriazol-1-yloxy*tris*(pyrrolidino)phosphonium hexafluorophosphate (PyAOP) were purchased from PerSeptive Biosystems U.K. Ltd.

Example 1

N-Hydroxy 2-({methyl[(biphen-4-yl)methyl]amino}sulfonyl)acetamide

[0089]



(a) Methyl 2-({methyl[biphen-4-yl)methyl]amino}sulfonyl)acetate

[0090] *N*-Methyl-*N*-[(biphen-4-yl)methyl]amine (Preparation 1, 500 mg, 2.5 mmol) and 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU, 0.38 ml, 2.5 mmol) were dissolved in dichloromethane (5 ml) and cooled to 0°C. Methyl chlorosulfonylacetate (0.44 g, 2.5 mmol) in dichloromethane (5 ml) was added dropwise to the solution, and the stirred mixture was allowed to warm to ambient temperature for 20 hours. The mixture was diluted with dichloromethane and washed with aqueous phosphate buffer (at pH 7), dried ($MgSO_4$), and the solvents were evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (dichloromethane as eluent) and the isolated product was crystallised from diisopropyl ether to give the title compound as a colourless solid (388 mg).

m.p. 82-84°C
^{1}H NMR (400 MHz, $CDCl_3$): 2.90 (s, 3H), 3.86 (s, 3H), 4.05 (s, 2H), 4.46 (s, 2H), 7.33-7.40 (m, 1H), 7.40-7.45 (m, 4H), 7.54-7.67 (m, 4H).
LRMS (Thermospray): 334.8 (MH^+).

(b) *N*-Hydroxy-2-({methyl[(biphen-4-yl)methyl]amino}sulfonyl)acetamide

[0091] Potassium carbonate (124 mg, 0.9 mmol) was added to a mixture of methyl 2-({methyl[(biphen-4-yl)methyl] amino}sulfonyl)acetate (100 mg, 0.3 mmol) and hydroxylamine hydrochloride (63 mg, 0.9 mmol) in methanol (3 ml). The mixture was heated to reflux for 18 hours. The mixture was cooled and partitioned between ethyl acetate and 0.1M aqueous hydrochloric acid. The layers were separated, and the organic layer was dried ($MgSO_4$), and the solvents were removed under reduced pressure. The residue was triturated with diisopropyl ether to give the titled compound as a colourless solid (88 mg).

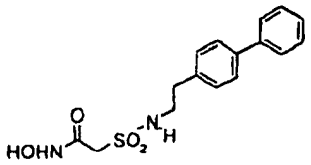
m.p. 176-178°C
^{1}H NMR (300 MHz, DMSO-d_6): 2.75 (s, 3H), 3.98 (s, 2H), 4.33 (s, 2H), 7.33-7.52 (m, 5H), 7.61-7.74 (m, 4H), 9.22 (s, 1H), 10.84 (br s, 1H).
LRMS (Thermospray): 335.7 (MH^+)

Analysis:	Found	C, 57.32;	H, 5.40;	N, 8.24.
$C_{16}H_{18}N_2O_4S$	Requires	C, 57.47;	H, 5.43;	N, 8.38.

Example 2

N-Hydroxy 2-({[2-(biphen-4-yl)ethyl]amino}sulfonyl)acetamide

[0092]



(a) Methyl 2-({[2-(biphen-4-yl)ethyl]amino}sulfonyl)acetate

[0093] In a manner similar to Example 1 (a), 2-(biphen-4-yl)ethylamine (Preparation 2) was reacted with methyl chlorosulfonylacetate to give the title compound as a colourless solid.

m.p. 130-131°C
^{1}H NMR (300 MHz, $CDCl_3$): 2.97 (t, 2H), 3.49 (q, 2H), 3.76 (s, 3H), 3.93 (s, 2H), 4.76 (br t, 1H), 7.22-7.40 (m, 3H), 7.40-7.50 (m, 2H), 7.52-7.64 (m, 4H).
LRMS (Thermospray): 351.1 (MNH_4^+)

Analysis:	Found	C, 61.39;	H, 5.74;	N, 4.19.
$C_{17}H_{19}NO_4S$,	Requires	C, 61.24;	H, 5.74;	N, 4.20.

(b) *N*-Hydroxy 2-({[2-(biphen-4-yl)ethyl]amino}sulfonyl)acetamide

[0094] In a manner similar to Example 1 (b), methyl 2-({[2-(biphen-4-yl)ethyl]amino}sulfonyl)acetate was reacted with hydroxylamine to give the title compound as a colourless solid.

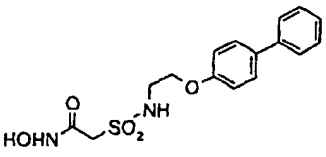
m.p. 202-204°C
^{1}H NMR (300 MHz, DMSO-d_6): 2.81 (t, 2H), 3.16-3.29 (m, 2H), 3.78 (s, 2H), 7.24-7.39 (m, 3H), 7.40-7.50 (m, 2H), 7.54-7.68 (m, 4H), 9.13 (s, 1H), 10.74 (br s, 1H).
LRMS (Thermospray): 336.2 (MH^+)

Analysis:	Found	C, 57.45;	H, 5.40;	N, 8.35.
$C_{16}H_{18}N_2O_4S$	Requires	C, 57.47;	H, 5.43;	N, 8.38.

Example 3

N-Hydroxy 2-({[2-(biphen-4-yloxy)ethyl]amino}sulfonyl)acetamide

[0095]



(a) Methyl 2-({[2-(biphen-4-yloxy)ethyl]amino}sulfonyl)acetate

[0096] In a manner similar to Example 1 (a), 2-(biphen-4-yloxy)ethylamine (Preparation 3) was reacted with methyl chlorosulfonylacetate to give the title compound as a colourless solid.

m.p. 123-124°C
^{1}H NMR (400 MHz, $CDCl_3$): 3.62 (q, 2H), 3,79 (s, 3H), 4.10 (s, 2H), 4.18 (t, 2H), 5.26 (br t, 1H), 6.98 (d, 2H), 7.31-7.34 (m, 1H), 7.39-7.46 (m, 2H), 7.50-7.60 (m, 4H).

Analysis:	Found	C, 58.33;	H, 5.44;	N, 3.99.
$C_{17}H_{19}NO_5S$	Requires	C, 58.43;	H, 5.48;	N, 4.01.

(b) *N*-Hydroxy 2-({[2-(biphen-4-yloxy)ethyl]amino}sulfonyl)acetamide

[0097] In a manner similar to Example 1 (b), methyl 2-({[2-(biphen-4-yloxy)ethyl]amino} sulfonyl)acetate was reacted with hydroxylamine to give the title compound as a colourless solid.

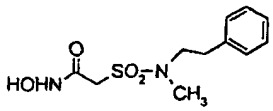
m.p. 222-224°C
^{1}H NMR (400 MHz, DMSO-d_6): 3.39 (d, 2H), 3.86 (s, 2H), 4.07 (t, 2H), 7.07 (d, 2H), 7.29-7.33 (m, 1H), 7.37-7.51 (m, 3H), 7.57-7.65 (m, 4H), 9.13 (s, 1H), 10.73 (s, 1H).
LRMS (Thermospray): 352.0 (MH^+)

Analysis:	Found	C, 54.69;	H, 5.13;	N, 7.92.
$C_{19}H_{22}N_2O_4S$	Requires	C, 54.84;	H, 5.18;	N, 8.00.

Example 4

N-Hydroxy 2-[methyl(phenethyl)amino]sulfonylacetamide

[0098]



(a) Methyl 2-[methyl(phenethyl)amino]sulfonylacetate

[0099] In a manner similar to Example 1 (a), *N*-methyl-*N*-phenethylamine was reacted with methyl chlorosulfonylacetate to give the titled compound as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): 2.88-2.96 (m, 5H), 3.48 (t, 2H), 3.77 (s, 3H), 3.81 (s, 2H), 7.18-7.36 (m, 5H).

(b) *N*-Hydroxy 2-[methyl(phenethyl)amino]sulfonylacetamide

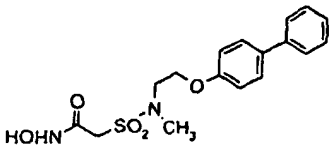
[0100] In a manner similar to Example 1 (b), methyl 2-[methyl(phenethyl)amino]sulfonylacetate was reacted with hydroxylamine to give the title compound as a colourless solid.

m.p. 149-151°C
^{1}H NMR (300 MHz, DMSO-d_6): 2.76-2.86 (m, 5H), 3.28 (s, 2H), 3.80 (s, 2H), 7.15-7.35 (m, 5H), 9.14 (s, 1H), 10.73 (s, 1H).
LRMS (Thermospray): 290.0 (MNH_4^+)
$C_{11}H_{16}N_2O_4S$.

Example 5

N-Hydroxy 2-({methyl-[2-(biphen-4-yloxy)ethyl]amino}sulfonyl)acetamide

[0101]



(a) Methyl 2-({methyl-[2-(biphen-4-yloxy)ethyl]amino}sulfonyl)acetate

[0102] Sodium hydride (23 mg of 60% dispersion in mineral oil, 0.58 mmol) was added to a stirred solution of methyl 2-({[2-(biphen-4-yloxy)ethyl]amino}sulfonyl)acetate (Example 3(a), 185 mg, 0.53 mmol) in anhydrous dimethylformamide (2 ml) at ambient temperature under a nitrogen atmosphere. After 30 minutes methyl *p*-toluenesulfonate (0.99 g, 0.53 mmol) was added, and stirring continued for an additional 3 hours. The mixture was partitioned between ethyl acetate and aqueous phosphate buffer (pH 7). The organic layer was separated and washed with water, dried ($MgSO_4$) and the solvents were removed under reduced pressure. The residue was crystallised from diisopropyl ether to give the titled compound as a colourless solid (170 mg).

m.p. 73-75°C
^{1}H NMR (400 MHz, $CDCl_3$): d = 3.11 (s, 3H), 3.69 (t, 2H), 3,78 (s, 3H), 4.08 (s, 2H), 4.18 (t, 2H), 6.97 (d, 2H), 7.28-7.32 (m, 1H), 7.38-7.46 (m, 2H), 7.47-7.58 (m, 4H).
LRMS (Thermospray): 381.1 (MNH_4^+)

Analysis:	Found	C, 59.39;	H, 5.88;	N, 3.74.
$C_{18}H_{21}NO_5S$	Requires	C,59.48;	H, 5.82;	N, 3.86.

(b) *N*-Hydroxy 2-({methyl-[2-(biphen-4 yloxy)ethyl]amino}sulfonyl)acetamide

[0103] In a manner similar to Example 1 (b), methyl 2-({methyl-[2-(biphen-4-yloxy)ethyl] amino}sulfonyl)acetate was reacted with hydroxylamine to give the title compound as a colourless solid.

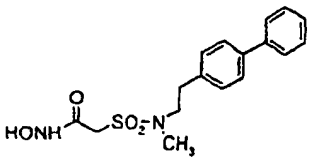
m.p. 153-155°C
^{1}H NMR (400 MHz, DMSO-d_6): d = 2.93 (s, 3H), *3.47-3.58* (m, 2H), 3.90 (s, 2H), 4.10-4.20 (m, 2H), 7.03 (d, 2H), 7.25-7.33 (m, 1H), 7.37-7.46 (m, 2H), 7.54-7.66 (m, 4H), 9.18 (s, 1H), 10.79 (s, 1H).
LRMS (APCI): 368.8 (MH^+)

Analysis:	Found	C, 55.56;	H, 5.47;	N, 7.24.
$C_{17}H_{20}N_2O_5S$	Requires	C, 56.03;	H, 5.53;	N, 7.69.

Example 6

N-Hydroxy 2-({methyl-[2-(biphen-4-yl)ethyl]amino}sulfonyl)acetamide

[0104]



(a) Methyl 2-({methyl-[2-(biphen-4-yl)ethyl]amino}sulfonyl)acetate

[0105] In a manner similar to Example 5 (a), methyl 2-({[2-(biphen-4-yl)ethyl]amino}-sulfonyl)acetate (Example 2 (a)) was reacted with sodium hydride and methyl *p*-toluenesulfonate to give the title compound as a colourless solid.

m.p. 72-74°C
^{1}H NMR (400 MHz, $CDCl_3$): 2.87-2.97 (m, 5H), 3.48 (t, 2H), 3.75 (s, 3H), 3.82 (s, 2H), 7.24-7.33 (m, 3H), 7.37-7.44 (m, 2H), 7.47-7.59 (m, 4H).
LRMS (Thermospray): 365.0 (MNH_4^+)
$C_{18}H_{21}NO_4S$

(b) *N*-Hydroxy 2-({methyl-[2-(biphen-4-yl)ethyl]amino}sulfonyl)acetamide

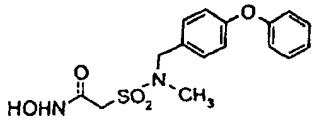
[0106] In a manner similar to Example 1 (b), methyl 2-({methyl-[2-(biphen-4-yl)ethyl] amino}sulfonyl)acetate was reacted with hydroxylamine to give the title compound as a colourless solid.

m.p. 166-168°C
^{1}H NMR (400 MHz, DMSO-d_6): 2.77-2.88 (m, 5H), 3.32 (t, 2H), 3.78 (s, 2H), 7.24-7.33 (m, 3H), 7.37-7.45 (m, 2H), 7.53-7.63 (m, 4H).
LRMS (Thermospray): 365.9 (MNH_4^+)
$C_{17}H_{20}N_2O_4S$.

Example 7

N-Hydroxy 2-({methyl[4-phenoxybenzyl]amino}sulfonyl)acetamide

[0107]



(a) Methyl 2-({methyl[4-phenoxybenzyl]amino}sulfonyl)acetate

[0108] In a manner similar to Example 1 (a), *N*-methyl-*N*-(4-phenoxybenzyl)amine (Preparation 4) was reacted with methyl chlorosulfonylacetate to give the title compound as a colourless solid.

m.p. 63-64°C
^{1}H NMR (300 MHz, $CDCl_3$): 2.84 (s, 3H), 3.81 (s, 3H), 4.00 (s, 2H), 4.35 (s, 2H), 6.95-7.06 (m, 4H), 7.06-7.16 (m, 1H), 7.21-7.40 (m, 4H).

LRMS (Thermospray): 350.6 (MH^+)
$C_{17}H_{19}NO_5S$.

(b) *N*-Hydroxy 2-({methyl[4-phenoxybenzyl]amino}sulfonyl)acetamide

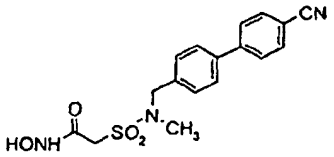
[0109] In a manner similar to Example 1(b), methyl 2-({methyl[4-phenoxybenzyl]amino}sulfonyl) acetate was reacted with hydroxylamine to give the title compound as a colourless solid.

m.p. 154-157°C
^{1}H NMR (400 MHz, DMSO-d_6): d = 2.72 (s, 3H), 3.95 (s, 2H), 4.26 (s, 2H), 6.94-7.04 (m, 4H), 7.10-7.18 (m, 1H), 7.29-7.43 (m, 4H).
LRMS (Thermospray): 373.5 (MNa^+)

Example 8

N-Hydroxy 2-({methyl[(4'-cyanobiphen-4-yl)methyl]amino}sulfonyl)acetamide

[0110]



(a) Methyl 2-({methyl[(4-bromophenyl)methyl]amino}sulfonyl)acetate

[0111] In a manner similar to Example 1(a), *N*-methyl-*N*-(4-bromobenzyl)amine (Preparation 5) was reacted with methyl chlorosulfonylacetate to give the title compound as a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): 2.83 (s, 3H), 3.82 (s, 3H), 4.03 (s, 2H), 4.33 (s, 2H), 7.25 (d, 2H), 7.50 (d, 2H).
LRMS (Thermospray): 354.3 (MNH_4^+)
$C_{11}H_{14}BrNO_4S$.

(b) Methyl-2-({methyl[(4'-cyanobiphen-4-yl)methyl]amino}sulfonyl)acetate

[0112] To a solution of methyl 2-({methyl[(4-bromophenyl)methyl]amino}sulfonyl)acetate (300 mg, 0.9 mmol) in dimethoxyethane (5 ml) was added 4-cyanophenylboronic acid (Preparation 6, 150 mg, 1.0 mmol), caesium fluoride (290 mg), tri-*ortho*-tolyl phosphine (28 mg, 0.09 mmol) and bis(benzylideneacetone)palladium(0) (25 mg, 0.04 mmol) and the mixture was heated to reflux for 1 hour under an atmosphere of nitrogen. The mixture was cooled to ambient temperature, diluted with dichloromethane (30 ml) and washed with water. The organic layer was dried (Na_2SO_4), the solvent was evaporated under reduced pressure and the residue was purified by flash chromatography on silica gel (hexane/ethyl acetate 2:1 as eluent) to give the titled compound as a pale yellow low melting solid (230mg).

^{1}H NMR (300 MHz, $CDCl_3$): 2.88 (s, 3H), 3.84 (s, 3H), 4.06 (s, 2H), 4.45 (s, 2H), 7.48 (d, 2H), 7.60 (d, 2H), 7.67 (d, 2H), 7.75 (d, 2H).

(c) 2-({methyl[(4'-cyanobiphen-4-yl)methyl]amino}sulfonyl)acetic acid

[0113] To a solution of methyl-2-({methyl[(4'-cyanobiphen-4-yl)methyl]amino}sulfonyl)acetate (200 mg, 0.56 mmol) in methanol (2 ml) and tetrahydrofuran (5 ml) was added 1M aqueous sodium hydroxide solution (1.2 ml, 1.2 mmol) and the mixture was stirred at ambient temperature for 2 hours. The solution was diluted with water (10 ml), acidified to pH 2 with 2M aqueous hydrochloric acid and extracted with dichloromethane (2 x 30 ml). The combined organic layers were dried (Na_2SO_4), and the solvent was evaporated under reduced pressure to give the title compound as a pale yellow solid (130 mg).

m.p. 149-152°C
^{1}H NMR (300 MHz, DMSO-d_6): 2.74 (s, 3H), 4.16 (s, 2H), 4.57 (s, 2H), 7.46 (d, 2H), 7.78 (d, 2H), 7.87 (d, 2H), 7.90 (d, 2H).

(d) *N*-Hydroxy 2-({methyl[(4'-cyanobiphen-4-yl)methyl]amino}sulfonyl)acetamide

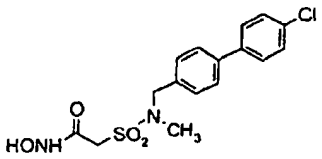
[0114] *O*-(7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU 263 mg, 0.72 mmol) was added to a solution of 2-({methyl[(4'-cyanobiphenyl-4-yl)methyl]amino}sulfonyl)acetic acid (185 mg, 0.48 mmol) and *N*-ethyl-N,N-diisopropylamine (0.08 ml, 0.48 mmol) in anhydrous dimethylformamide (3 ml) at ambient temperature under an atmosphere of nitrogen. After stirring for 20 minutes a solution of hydroxylamine hydrochloride (131 mg, 1.92 mmol) and *N*-ethyl-*N,N*-diisopropylamine (0.33 ml, 1.92 mmol) in anhydrous dimethylformamide (1 ml) was added and the solution was stirred for a further 16 hours. The mixture was partitioned between aqueous phosphate buffer (at pH 7) and ethyl acetate. The organic layer was washed with water, dried (MgSO4) and the solvent evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (dichloromethane/methanol/aqueous ammonia 90:10:1 as eluent) to give the title compound as a colourless solid (14 mg).

m.p. 128-130°C
^{1}H NMR (400 MHz, DMSO-d_6): 2.73 (s, 3H), 3.97 (s, 2H), 4.33 (s, 2H), 7.44 (d, 2H), 7.74 (d, 2H), 7.85 (d, 2H), 7.91 (d, 2H).
LRMS (Thermospray): 361.0 ($M+2H^+$).

Example 9

N-Hydroxy 2-({methyl[(4'-chlorobiphen-4-yl)methyl]amino}sulfonyl)acetamide

[0115]



(a) Methyl-2-({methyl[(4'-chlorobiphen-4-yl)methyl]amino}sulfonyl)acetate

[0116] In a manner similar to Example 8 (b), methyl 2-({methyl[(4'-bromophenyl-4-yl)methyl]amino}sulfonyl)acetate (Example 8 (a)) was reacted with 4-chlorophenylboronic acid to give the titled compound as a pale yellow solid.

m.p. 103-106°C
^{1}H NMR (400 MHz, $CDCl_3$): 2.87 (s, 3H), 3.83 (s, 3H), 4.04 (s, 2H), 4.43 (s, 2H), 7.38-7.46 (m, 4H), 7.48-7.59 (m, 4H).
LRMS (Thermospray): 385.2 ($M+H^+$)

(b) *N*-Hydroxy-2-({methyl[(4'-chlorobiphen-4-yl)methyl]amino}sulfonyl)acetamide

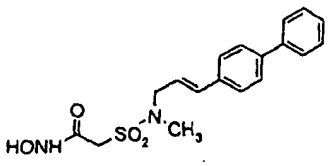
[0117] In a manner similar to Example 1 (b), methyl-2-({methyl[(4'-chlorobiphenyl-4-yl)methyl]amino}sulfonyl)acetate was reacted with hydroxylamine to give the title compound as a colourless solid.

m.p. 158-161°C
^{1}H NMR (400 MHz, DMSO-d_6): 2.72 (s, 3H), 3.95 (s, 2H), 4.32 (s, 2H), 7.40 (d, 2H), 7.49 (d, 2H), 7.66 (d, 2H), 7.69 (d, 2H), 9.22 (s, 1H), 10.83 (s, 1H).
LRMS (Thermospray): 369.8 ($M+H^+$).

Example 10

N-Hydroxy 2-({methyl[3-(biphen-4-yl)-*trans*-prop-2-enyl]amino}sulfonyl)acetamide

[0118]



(a) Methyl 2-({methyl[allyl]amino}sulfonyl)acetate

[0119] In a manner similar to Example 1 (a), *N*-methyl-*N*-allylamine was reacted with methyl chlorosulfonylacetate to give the title compound as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): 2.89 (s, 3H), 3.81 (s, 3H), 3.81 (d, 2H), 3.97 (s, 2H), 5.03-5.15 (m, 2H), 5.74-5.88 (m, 1H).

(b) Methyl-2-({methyl[3-(biphen-4-yl)-*trans*-prop-2-enyl]amino}sulfonyl)acetate

[0120] To a solution of methyl 2-({methyl[allyl]amino}sulfonyl)acetate (300 mg, 1.4 mmol) and 4-bromobiphenyl (370 mg, 1.54 mmol) in acetonitrile (4 ml) was added triethylamine (0.3 ml, 2.1 mmol), palladium(II) acetate (17 mg, 0.07 mmol) and tri-*ortho*-tolyl phosphine (52 mg, 0.14 mmol) and the solution was heated to reflux under an atmosphere of nitrogen for 3 hours. The mixture was cooled to ambient temperature, the solvent was evaporated and the residue was purified by flash chromatography on silica gel (dichloromethane as eluent) to give the title compound as a pale yellow solid (300 mg).

m.p. 104-107°C
^{1}H NMR (300 MHz, $CDCl_3$): 2.97 (s, 3H), 3.86 (s, 3H), 4.00-4.13 (m, 4H), 6.24 (dt, 1H), 6.66 (d, 1H), 7.33-7.40 (m, 1H), 7.41-7.54 (m, 4H), 7.58-7.71 (m, 4H).
LRMS (Thermospray): 377.2 (MNH_4^+).

(c) *N*-Hydroxy-2-({methyl[3-(biphen-4-yl)-*trans*-prop-2-enyl]amino}sulfonyl)acetamide

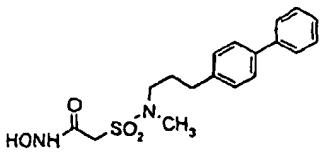
[0121] In a manner similar to Example 1 (b), methyl 2-({methyl[3-(1,1'-biphenyl-4-yl)-*trans*-prop-2-enyl]amino}sulfonyl)acetate was reacted with hydroxylamine to give the title compound as a colourless solid.

m.p. 153-155°C
^{1}H NMR (300 MHz, DMSO-d_6): 2.82 (s, 3H), 3.88-3.97 (m, 4H), 6.34 (dt, 1H), 6.66 (d, 1H), 7.36 (d, 1H), 7.43 (d, 1H), 7.46 (d, 1H), 7.56 (d, 2H), 7.64 (d, 2H), 7.67 (d, 2H), 9.20 (s, 1H), 10.81 (s, 1H).
LRMS (Thermospray): 362.2 ($M+2H^+$).

Example 11

N-Hydroxy 2-({methyl[3-(biphen-4-yl)-prop-1-yl]amino}sulfonyl)acetamide

[0122]



(a) Methyl-2-({methyl[3-(biphen-4-yl)-propyl]amino}sulfonyl)acetate

[0123] To a solution of methyl- 2-({methyl[3-(biphen-4-yl)-*trans*-prop-2-enyl]amino}sulfonyl)acetate (Example 10 (b), 200 mg, 0.56 mmol) and ammonium formate (175 mg, 2.8 mmol) in methanol (5 ml) was added 20% palladium hydroxide on carbon (50 mg) and the mixture was heated to reflux for 4 hours. The mixture was cooled to ambient temperature, filtered through arbocel and the filtrate was concentrated under reduced pressure to give the title compound as a pale yellow solid (193 mg).

m.p. 66-70°C
^{1}H NMR (300 MHz, $CDCl_3$): 1.89-2.04 (m, 2H), 2.72 (t, 2H), 2.95 (s, 3H), 3.30 (t, 2H), 3.80 (s, 3H), 3.97 (s, 2H), 7.23-7.38 (m, 3H), 7.40-7.47 (m, 2H), 7.54 (d, 2H), 7.59 (d, 2H).
LRMS (Thermospray): 379.2 (MNH_4^+).

(b) *N*-Hydroxy 2-({methyl[3-(biphen-4-yl)-propyl]amino}sulfonyl)acetamide

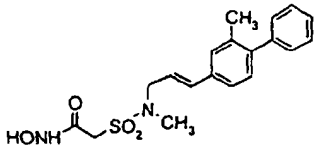
[0124] In a manner similar to Example 1 (b), methyl-2-({methyl[3-(biphen-4-yl)-propyl]amino}sulfonyl)acetate was reacted with hydroxylamine to give the title compound as a colourless solid.

m.p. 137-140°C
^{1}H NMR (300 MHz, DMSO-d_6): 1.75-1.93 (m, 2H), 2.61 (t, 2H), 2.82 (s, 3H), 3.18 (t, 2H), 3.83 (s, 2H), 7.25-7.36 (m, 3H), 7.40-7.50 (m, 2H), 7.57 (d, 2H), 7.64 (d, 2H), 9.05-9.28 (br s, 1H).
LRMS (Thermospray): 380.2 (MNH_4^+).

Example 12

N-Hydroxy 2-({methyl-[3-(2-methylbiphen-4-yl)-*trans*-prop-2-enyl]amino}sulfonyl)acetamide

[0125]



(a) Methyl 2-({methyl-[3-(2-methylbiphen-4-yl)-*trans*-prop-2-enyl]amino}sulfonyl)acetate

[0126] In a manner similar to Example 10 (b), methyl 2-({methyl[allyl]amino}sulfonyl)acetate (Example 10 (a)) was reacted with 4-bromo-2-methylbiphenyl (Preparation 7) to give the title compound as a pale yellow low melting solid.

^{1}H NMR (400 MHz, $CDCl_3$): 2.29 (s, 3H), 2.97 (s, 3H), 3.93 (s, 3H), 4.00-4.07 (m, 4H), 6.23 (dt, 1H), 6.62 (d, 1H),

7.18-7.47 (m, 8H).
LRMS (Thermospray): 391.9 (MNH_4^+).

(b) *N*-Hydroxy 2-({methyl-[3-(2-methylbiphen-4-yl)-*trans*-prop-2-enyl]amino}sulfonyl)acetamide

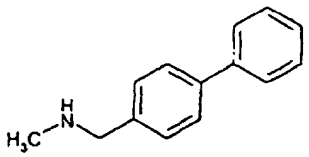
[0127] In a manner similar to Example 1 (b), methyl 2-({methyl-[3-(2-methylbiphen-4-yl)-*trans*-prop-2-enyl]amino} sulfonyl)acetate was reacted with hydroxylamine to give the titled compound as a colourless solid.

m.p. 146-149°C
^{1}H NMR (400 MHz, DMSO-d_6): 2.23 (s, 3H), 2.81 (s, 3H), 3.82-4.02 (m, 4H), 6.33 (dt, 1H), 6.62 (d, 1H), 7.17 (d, 1H), 7.25-7.49 (m, 7H), 9.21 (s, 1H), 10.82 (s, 1H).
LRMS (Thermospray): 376.1 ($M+2H^+$)

Preparation 1

N-Methyl-*N*-[(biphen-4-yl)methyl]amine

[0128]



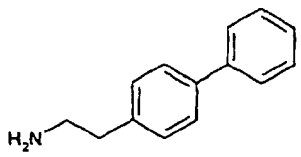
[0129] To a solution of biphenyl-4-carboxaldehyde (4.6 g, 25 mmol) in ethanol (50 ml) was added methylamine (3.0 ml of 33% solution in ethanol, 25 mmol) and acetic acid (1.4 ml, 25 mmol), and the mixture was stirred under an atmosphere of nitrogen. After 20 minutes sodium tri(acetoxy)borohydride (10.5 g, 50 mmol) was added and stirring was continued for 16 hours. The mixture was diluted with 2M aqueous hydrochloric acid (200 ml) and washed with ethyl acetate (3 x 100 ml). The aqueous layer was basified to pH 12 with concentrated aqueous ammonia solution and extracted with dichloromethane (4 x 100 ml). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated under reduced pressure to give the title compound as a pale yellow oil (2.5 g).

^{1}H NMR (300 MHz, $CDCl_3$):1.38 (br s, 1H), 2.50 (s, 3H), 3.80 (s, 2H), 7.30-7.48 (m, 5H), 7.52-7.64 (m, 4H).

Preparation 2

2-(Biphen-4-yl)ethylamine

[0130]

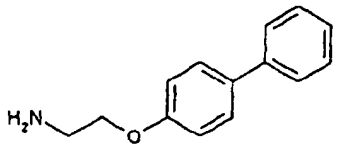


[0131] This was prepared according to the method described by W. W. Zacac Jr, J. F. Siuda, M. J. Nolan and T. M. Santususso, in *J. Org. Chem.* 1971, *36*, 3539.

Preparation 3

2-(Biphen-4-yloxy)ethylamine

[0132]



(a) 2-([Biphen-4-yloxy]ethyl)isoindoline-1,3-dione

[0133] Potassium phthalimide (1.2 g, 6.5 mmol) was added to a solution of 4-(2-chloroethoxy)-1,1'-biphenyl (1.0 g, 5.4 mmol) in anhydrous dimethylformamide (3 ml) and anhydrous dimethylsulfoxide (3 ml) and the mixture was heated to 70°C under an atmosphere of nitrogen for 5 hours. The mixture was cooled to ambient temperature and partitioned between water and dichloromethane. The organic layer was washed with water, dried (Na_2SO_4) and the solvent was evaporated under reduced pressure to give the title compound as a colourless solid (1.51 g).

^{1}H NId:R (300 MHz, $CDCl_3$): 4.13 (t, 2H), 4.26 (t, 2H), 6.96 (d, 2H), 7.23-7.34 (m, 1H), 7.34-7.44 (m, 2H), 7.44-7.58 (m, 4H), 7.67-7.80 (m, 2H), 7.83-7.93 (m, 2H).
LRMS (Thermospray): 343.3 (M^+).

(b) 2-(Biphen-4-yloxy)ethylamine

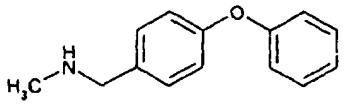
[0134] To a solution of 2-([biphen-4-yloxy]ethyl)isoindoline-1,3-dione (1.5 g, 4.4 mmol) in dichloromethane (30 ml) was added methylamine (33% solution in ethanol, 50 ml) and the solution was heated to reflux under an atmosphere of nitrogen for 2 hours. The mixture was cooled to ambient temperature, and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (dichloromethane/methanol/aqueous ammonium solution 95:5:0 to 94:5:1 as eluent) to give the title compound as a colourless solid (505 mg).

^{1}H NMR (400 MHz, $CDCl_3$): 1.40 (s, 2H), 3.05-3.19 (m, 2H), 3.98-4.12 (m, 2H), 6.98 (d, 2H), 7.22-7.66 (m, 7H).
LRMS (Thermospray): 214.0 (MH^+).

Preparation 4

N-Methyl-*N*-(4-phenoxybenzyl)amine

[0135]



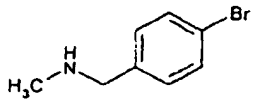
[0136] To a solution of 4-phenoxybenzaldehyde (4.4 ml, 25 mmol) in ethanol (50 ml) was added methylamine (3.0 ml of 33% solution in ethanol, 25 mmol) and acetic acid (1.4 ml, 25 mmol), and the mixture was stirred under an atmosphere of nitrogen. After 20 minutes sodium tri(acetoxy)borohydride (10.5 g, 50 mmol) was added and stirring was continued for 16 hours. The mixture was diluted with 2M aqueous hydrochloric acid (200 ml) and washed with diethyl ether (2 x 100 ml). The aqueous layer was basified to pH 12 with concentrated aqueous ammonia solution and extracted with dichloromethane (4 x 100ml). The combined organic layers were dried (Na_2SO_4), the solvent was evaporated under reduced pressure and the residue was purified by flash chromatography on silica gel (dichloromethane/methanol/aqueous ammonia solution 95:5:0 to 94:5:1) to give the titled compound as a colourless oil (3.3 g).

^{1}H NMR (300 MHz, $CDCl_3$): 2.33 (s, 1H), 2.47 (s, 3H), 3.73 (s, 2H), 6.93-7.02 (m, 4H), 7.02-7.13 (m, 1H), 7.23-7.37 (m, 4H).

Preparation 5

N-Methyl-*N*-(4-bromobenzyl)amine

[0137]

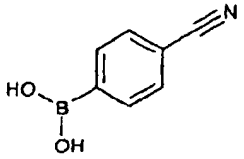


[0138] This was prepared according to the method of G. M. Singer et al, described in *J. Med. Chem.* 1986, *29,* 40.

Preparation 6

4-Cyano-phenylboronic acid

[0139]

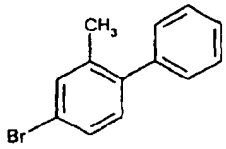


[0140] This was prepared according to the method of G. J. Pernia et al, described in *J. Am. Chem. Soc.* 1996, *118,* 10220.

Preparation 7

4-Bromo-2-methylbiphenyl

[0141]



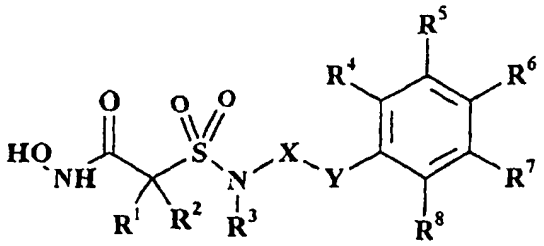
[0142] This was prepared according to the method of M. Gomberg et al, described in *J. Am Chem. Soc.* 1926, *48,* 1372.

Biological Data

[0143] The substances of Examples 1-12 had MMP-3 IC_{50} values of 1.5μM or less. The substances of Examples 1-12 had MMP-2 IC_{50} values of 6.3μM or less. Certain of the substances of the Examples had MMP-13 IC_{50} values of 0.05μM or less.

Claims

1. A compound of formula (I):



(I)

and a pharmaceutically- and/or veterinarily-acceptable salt thereof, and a solvate of such compound and salt, wherein

R^1 and R^2 are each independently H,
C_{2-6} alkenyl, aryl(C_{1-6} alkyl), heteroaryl(C_{1-6} alkyl), aryloxy(C_{1-6} alkyl), heteroaryloxy-(C_{1-6} alkyl),
C_{1-6} alkyl optionally substituted by NH_2, C_{1-6} acylamino, OH, or by CO_2H,
or R^1 and R^2 can be taken together with the carbon atom to which they are attached, to form a 4- to 8-membered saturated carbocyclic or heterocyclic ring, which heterocyclic ring has 1 or 2 hetero-groups selected from O, $S(O)_n$ or NR^9 in the ring,
R^3 is H, C_{1-6} alkyl or (C_{1-6} alkoxy)C_{1-6} alkyl,
R^4, R^5, R^7 and R^8 are each independently H, C_{1-6} alkyl, C_{1-6} alkoxy, CN or halogen,
R^6 is H, aryl, heteroaryl, aryloxy or heteroaryloxy, C_{1-6} alkyl, C_{1-6} alkoxy, CN or halogen,
R^9 is H or C_{1-6} alkyl,
n is 0,1 or 2,
X is C_{1-6} alkylene or C_{2-6} alkenylene,
Y is a direct link, CH=CH or O,

wherein "aryl" is phenyl optionally fused with another ring selected from furan, dioxolan, and pyran, which group is optionally mono- or disubstituted by substituents independently seleceted from halogen, CN, C_{1-6} alkyl optionally substituted by OH or NH_2, C_{1-6} alkoxy, perfluoro(C_{1-6} alkyl) and perfluoro(C_{1-6} alkoxy), and wherein "heteroaryl" is a 5- or 6-membered aromatic heterocycle with one or two heteroatoms in the ring, which heteroatoms are independently selected from O, N and S, which heteroaryl is optionally mono- or disubstituted by substituents independently selected from halogen, CN, C_{1-6} alkyl optionally substituted by OH or NH_2, C_{1-6} alkoxy, perfluoro(C_{1-6} alkyl) and perfluoro(C_{1-6} alkoxy).

2. A substance according to claim 1 wherein R^1 is H.

3. A substance according to any preceding claim wherein R^2 is H.

4. A substance according to any preceding claim wherein R^3 is H or C_{1-6} alkyl.

5. A substance according to any preceding claim wherein R^4 is H.

6. A substance according to any preceding claim wherein R^5 is H or C_{1-6} alkyl.

7. A substance according to any preceding claim wherein R^6 is H, $aryl^1$ or $aryl^1oxy$ wherein "$aryl^1$" is phenyl optionally mono- or disubstituted by substituents selected from halogen and CN.

8. A substance according to any preceding claim wherein R^7 is H.

9. A substance according to any preceding claim wherein R^8 is H.

10. A substance according to any preceding claim wherein X is CH_2, $(CN_2)_2$, $(CN_2)_3$, or is $CH_2CH{=}CH$ wherein the terminal methinyl carbon of this group is linked to the Y moiety.

11. A substance according to any preceding claim wherein R^3 is H or CH_3.

12. A substance according to any preceding claim wherein $R^5$is H or CH_3.

13. A substance according to any preceding claim wherein R^6 is H, $aryl^2$ or $aryl^2$oxy wherein "$aryl^2$" is phenyl optionally 4-substituted by substituents selected from Cl and CN.

14. A substance according to any preceding claim wherein R^6 is H, phenyl, phenoxy, 4-cyanophenyl or 4-chlorophenyl.

15. A substance according to any preceding claim wherein at least two of the groups R^4, R^5, R^7 and R^8 are all H.

16. A substance according to any preceding claim wherein R^4, R^7 and R^8 are all H and R^5 is CH_3.

17. A substance according to any preceding claim wherein R^1, R^2, R^4, R^7 and R^8 are all H,

R^3 is H or CH_3,
$R^5$is H or CH_3,
R^6 is H, phenyl, phenoxy, 4-cyanophenyl or 4-chlorophenyl,
X is CH_2, $(CH_2)_2$, $(CH_2)_3$, or is $CH_2CH{=}CH$ wherein the terminal methine carbon of this group is linked to the Y moiety,
and the salts and solvates thereof.

18. A pharmaceutical composition comprising a substance according to any one of claims 1 to 17, together with a pharmaceutically acceptable diluent or carrier.

19. A veterinary composition comprising a substance according to any one of claims 1 to 17, together with a veterinarally acceptable diluent or carrier.

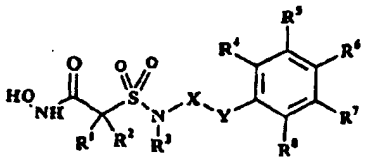
20. A substance according to any one of claims 1 to 17 for use as a medicament.

21. The use of a substance according to any one of claims 1 to 17 in the manufacture of a medicament for the treatment of a condition mediated by one or more MMPs.

22. The use of a substance according to any one of claims 1 to 17 in the manufacture of a medicament for the treatment of atherosclerotic plaque rupture, myocardial infarction, heart failure, restenosis, stroke, periodontal disease, tissue ulceration, wounds, skin diseases, cancer metastasis, tumour angiogenesis, age-related macular degeneration, fibrotic disease, rheumatoid arthritis, osteoarthritis and inflammatory diseases dependent on migratory inflammatory cells.

Patentansprüche

1. Verbindung der Formel (I):



(I)

und ein pharmazeutisch und/oder veterinär verträgliches Salz davon und ein Solvat einer solchen Verbindung und Salz,
worin R^1 und R^2 jeweils unabhängig H, C_{2-6}-Alkenyl, Aryl-(C_{1-6}-alkyl), Heteroaryl (C_{1-6}-alkyl), Aryloxy(C_{1-6}-alkyl), Heteroaryloxy-(C_{1-6}-alkyl), C_{1-6}-Alkyl, gegebenenfalls mit NH_2, C_{2-6}-Acylamino, OH oder mit CO_2H substituiert, darstellen oder R^1 und R^2 mit dem Kohlenstoffatom, an das sie gebunden sind, unter Bildung eines 4- bis 8-gliedrigen gesättigten carbocyclischen oder heterocyclischen Rings zusammengenommen werden können, wobei der heterocyclische Ring 1 oder 2 Heterogruppen, ausgewählt aus O, $S(O)_n$ oder NR^9, in dem Ring aufweist,

R^3 H, C_{1-6}-Alkyl oder (C_{1-6}-Alkoxy)C_{1-6}-alkyl darstellt,
R^4, R^5, R^7 und R^8 jeweils unabhängig H, C_{1-6}-Alkyl, C_{1-6}-Alkoxy, CN oder Halogen darstellen, R^6 H, Aryl, Heteroaryl, Aryloxy oder Heteroaryloxy, C_{1-6}-Alkyl, C_{1-6}-Alkoxy, CN oder Halogen darstellt,
R^9 H oder C_{1-6}-Alkyl darstellt,
n 0, 1 oder 2 ist,
X C_{1-6}-Alkylen oder C_{2-6}-Alkenylen darstellt,
Y eine direkte Bindung, CH=CH oder O, darstellt,

worin "Aryl" Phenyl, gegebenenfalls kondensiert mit einem weiteren Ring, ausgewählt aus Furan, Dioxolan und Pyran, darstellt, wobei die Gruppe gegebenenfalls mit Substituenten, unabhängig ausgewählt aus Halogen, CN, C_{1-6}-Alkyl, gegebenenfalls substituiert mit OH oder NH_2, C_{1-6}-Alkoxy, Perfluor(C_{1-6}-alkyl) und Perfluor(C_{1-6}-alkoxy), mono- oder disubstituiert ist,
und worin "Heteroaryl" einen 5- oder 6-gliedrigen aromatischen Heteocyclus mit ein oder zwei Heteroatomen in dem Ring darstellt, wobei die Heteroatome unabhängig aus O, N und S ausgewählt sind, wobei Heteroaryl gegebenenfalls mit Substituenten, unabhängig ausgewählt aus Halogen, CN, C_{1-6}-Alkyl, gegebenenfalls substituiert mit OH oder NH_2, C_{1-6}-Alkoxy, Perfluor(C_{1-6}-alkyl) und Perfluor(C_{1-6}-alkoxy) mono - oder disubstituiert ist.

2. Substanz nach Anspruch 1, worin R^1 H darstellt.

3. Substanz nach einem vorangehenden Anspruch, worin R^2 H darstellt.

4. Substanz nach einem vorangehenden Anspruch, worin R^3 H oder C_{1-6}-Alkyl darstellt.

5. Substanz nach einem vorangehenden Anspruch, worin R^4 H darstellt.

6. Substanz nach einem vorangehenden Anspruch, worin R^5 H oder C_{1-6}-Alkyl darstellt.

7. Substanz nach einem vorangehenden Anspruch, worin R^6 H, $Aryl^1$ oder $Aryl^1$oxy darstellt, worin "$Aryl^1$" Phenyl, gegebenenfalls mit Substituenten, ausgewählt aus Halogen und CN, mono- oder disubstituiert ist.

8. Substanz nach einem vorangehenden Anspruch, worin R^7 H darstellt.

9. Substanz nach einem vorangehenden Anspruch, worin R^8 H darstellt.

10. Substanz nach einem vorangehenden Anspruch, worin X CH_2, $(CH_2)_2$, $(CH_2)_3$ darstellt oder $CH_2CH{=}CH$ darstellt, worin das endständige Methinylkohlenstoffatom dieser Gruppe an die Y-Einheit gebunden ist.

11. Substanz nach einem vorangehenden Anspruch, worin R^3 H oder CH_3 darstellt.

12. Substanz nach einem vorangehenden Anspruch, worin R^5 H oder CH_3 darstellt.

13. Substanz nach einem vorangehenden Anspruch, worin R^6 H, $Aryl^2$ oder $Aryl^2$oxy darstellt, worin "$Aryl^2$" Phenyl, gegebenenfalls 4-substituiert mit Substituenten, ausgewählt aus Cl und CN, darstellt.

14. Substanz nach einem vorangehenden Anspruch, worin R^6 H, Phenyl, Phenoxy, 4-Cyanophenyl oder 4-Chlorphenyl darstellt.

15. Substanz nach einem vorangehenden Anspruch, worin mindestens zwei der Gruppen R^4, R^5, R^7 und R^8 alle H darstellen.

16. Substanz nach einem vorangehenden Anspruch, worin R^4, R^7 und R^8 alle H darstellen und R^5 CH_3 darstellt.

17. Substanz nach einem vorangehenden Anspruch, worin R^1, R^2, R^4, R^7 und R^8 alle H darstellen,

R^3 H oder CH_3 darstellt,
R^5 H oder CH_3 darstellt,
R^6 H, Phenyl, Phenoxy, 4-Cyanophenyl oder 4-Chlorphenyl darstellt,
X CH_2, $(CH_2)_2$, $(CH_2)_3$ darstellt oder $CH_2CH{=}CH$ darstellt,

worin das endständige Methinkohlenstoffatom dieser Gruppe an die Y-Einheit gebunden ist,
und die Salze und Solvate davon.

18. Pharmazeutische Zusammensetzung, umfassend eine Substanz nach einem der Ansprüche 1 bis 17, zusammen mit einem pharmazeutisch verträglichen Verdünnungsmittel oder Träger.

19. Veterinäre Zusammensetzung, umfassend eine Substanz nach einem der Ansprüche 1 bis 17, zusammen mit einem veterinär verträglichen Verdünnungsmittel oder Träger.

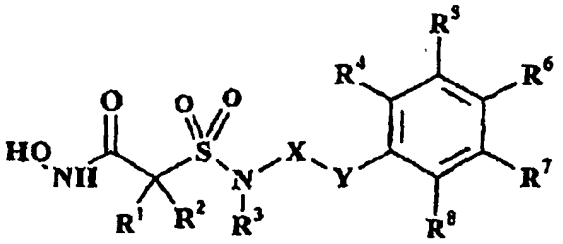
20. Substanz nach einem der Ansprüche 1 bis 17 zur Verwendung als Arzneimittel.

21. Verwendung einer Substanz nach einem der Ansprüche 1 bis 17 bei der Herstellung eines Arzneimittels zur Behandlung eines durch ein oder mehrere MMP vermittelten Zustands.

22. Verwendung einer Substanz nach einem der Ansprüche 1 bis 17 zur Herstellung eines Arzneimittels zur Behandlung von arterioskleroischem Plaquebruch, Herzinfarkt, Herzversagen, Restenose, Schlaganfall, Periodontalkrankheit, Gewebsulceration, Wunden, Hauterkrankungen, Krebsmetastasen, Tumorangiogenese, altersbedingter macularer Degeneration, fibrotischer Erkrankung, rheumatischer Arthritis, Osteoarthritis und entzündlichen Erkrankungen, die von wandernden entzündlichen Zellen abhängen.

Revendications

1. Composé de formule (1):



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et un sel acceptable pour une utilisation pharmaceutique et/ou vétérinaire, de celui-ci, et un solvate de ce composé et de ce sel,

où:

R^1 et R^2 sont chacun, indépendamment, H,
alcényle en C_{2-6}, aryle (alkyle en C_{1-6}), hétéroaryle (alkyle en C_{1-6}), aryloxy (alkyle en C_{1-6}) hetéroaryloxy (alkyle en C_{1-6}),
alkyle en C_{1-6}, éventuellement substitué par NH_2, acylamino en C_{2-6}, OH, ou par CO_2H,
ou R^1 et R^2 peuvent être pris avec l'atome de carbone auquel ils sont fixés pour former un cycle carbocyclique ou hétérocyclique saturé de 4 à 8 membres, lequel cycle hétérocyclique comporte 1 ou 2 hétérogroupes choisis parmi O, S(O)n ou NR^9 dans le cycle,

R^3 est H, alkyle en C_{1-6} ou (alcoxy en C_{1-6})alkyle en C_{1-6},
R^4, R^5, R^7 et R^8 sont chacun indépendamment H, alkyle en C_{1-6}, alcoxy en C_{1-6}, CN ou halogène,
R^6 est H, aryle, hétéroaryle, aryloxy ou hétéroaryloxy, alkyle en C_{1-6}, alcoxy en C_{1-6}, CN ou halogène,
R^9 est H ou alkyle en C_{1-6},
n est 0, 1 ou 2,
X est alkylène en C_{1-6}, ou alcénylène en C_{2-6},
Y est une liaison directe, CH=CH ou O,

où

"aryle" est phényle éventuellement condensé avec un autre cycle choisi parmi furanne, dioxolane et pyranne, lequel groupe est éventuellement mono- ou disubstitué par des substituants choisis indépendamment parmi halogène, CN, alkyle en C_{1-6} éventuellement substitué par OH ou NH_2, alcoxy en C_{1-6}, perfluoro (alkyle en C_{1-6}) et perfluoro (alcoxy en C_{1-6}),
et où "hétéroaryle" est un hétérocycle aromatique à 5 ou 6 membres avec un ou deux hétéroatomes dans le cycle, lesquels hétéroatomes sont choisis indépendamment parmi O, N et S, lequel hétéroaryle est éventuellement mono- ou disubstitué par des substituants choisis indépendamment parmi halogène, CN, alkyle en C_{1-6} éventuellement substitué par OH ou NH_2, alcoxy en C_{1-6}, perfluoro (alkyle en C_{1-6}) et perfluoro (alkoxy en C_{1-6}).

2. Substance selon la revendication 1 dans laquelle R^1 est H.

3. Substance selon l'une quelconque des revendications précédentes dans laquelle R^2 est H.

4. Substance selon l'une quelconque des revendications précédentes dans laquelle R^3 est H ou alkyle en C_{1-6}.

5. Substance selon l'une quelconque des revendications précédentes dans laquelle R^4 est H.

6. Substance selon l'une quelconque des revendications précédentes dans laquelle R^5 est H ou alkyle en C_{1-6}.

7. Substance selon l'une quelconque des revendications précédentes dans laquelle R^6 est H, aryle[1] ou aryl[1]oxy où "aryle" est phényle, éventuellement mono ou disubstitué par des substituants choisis parmi halogène et CN.

8. Substance selon l'une quelconque des revendications précédentes dans laquelle R^7 est H.

9. Substance selon l'une quelconque des revendications précédentes dans laquelle R^8 est H.

10. Substance selon l'une quelconque des revendications précédentes dans laquelle X est CH_2, $(CH_2)_2$, $(CH_2)_3$, ou est $CH_2CH=CH$ où le carbone du méthinyle terminal de ce groupe est lié au fragment Y.

11. Substance selon l'une quelconque des revendications précédentes dans laquelle R^3 est H ou CH_3.

12. Substance selon l'une quelconque des revendications précédentes dans laquelle R^5 est H ou CH_3.

13. Substance selon l'une quelconque des revendications précédentes dans laquelle R^6 est H, aryle[2] ou aryl[2]oxy où "aryle[2]" est phényle, éventuellement substitué en position 4 par des substituants choisis parmi Cl et CN.

14. Substance selon l'une quelconque des revendications précédentes dans laquelle R^6 est H, phényle, phénoxy, 4-cyanophényle ou 4-chlorophényle.

15. Substance selon l'une quelconque des revendications précédentes dans laquelle au moins deux des groupes R^4, R^5, R^7 et R^8 sont tous H.

16. Substance selon l'une quelconque des revendications précédentes dans laquelle R^4, R^7 et R^8 sont tous H et R^5 est CH_3.

17. Substance selon l'une quelconque des revendications précédentes dans laquelle R^1, R^2, R^4, R^7 et R^8 sont tous H,

R^3 est H ou CH_3,
R^5 est H ou CH_3,
R^6 est H, phényle, phénoxy, 4-cyanophényle ou 4-chlorophényle,
X est CH_2, $(CH_2)_2$, $(CH_2)_3$, ou $CH_2CH=CH$ où le carbone du méthinyle terminal de ce groupe est lié au fragment Y,

et les sels et solvates de cette dernière.

18. Composition pharmaceutique comprenant une substance selon l'une quelconque des revendications 1 à 17 avec un diluant ou un support acceptable pour une utilisation pharmaceutique.

19. Composition vétérinaire comprenant une substance selon l'une quelconque des revendications 1 à 17, avec un diluant ou un support acceptable pour une utilisation vétérinaire.

20. Substance selon l'une quelconque des revendications 1 à 17 pour utilisation comme médicament.

21. Utilisation d'une substance selon l'une quelconque des revendications 1 à 17 dans la fabrication d'un médicament pour le traitement d'un état **caractérisé par** une ou plusieurs MMP.

22. Utilisation d'une substance selon l'une quelconque des revendications 1 à 17 dans la fabrication d'un médicament pour le traitement de la rupture de plaque athérosclérotique, l'infarctus du myocarde, l'insuffisance cardiaque, la resténose, l'accident vasculaire cérébral , la parodontopathie, l'ulcération des tissus, les blessures, les maladies de la peau, les métastases du cancer, l'angiogénèse de tumeurs, la dégénérescence maculaire liée à l'âge, les maladies fibrotiques, la polyarthrite rhumatoïde, l'ostéoarthrite et les maladies inflammatoires dépendantes de cellules inflammatoires migratoires.

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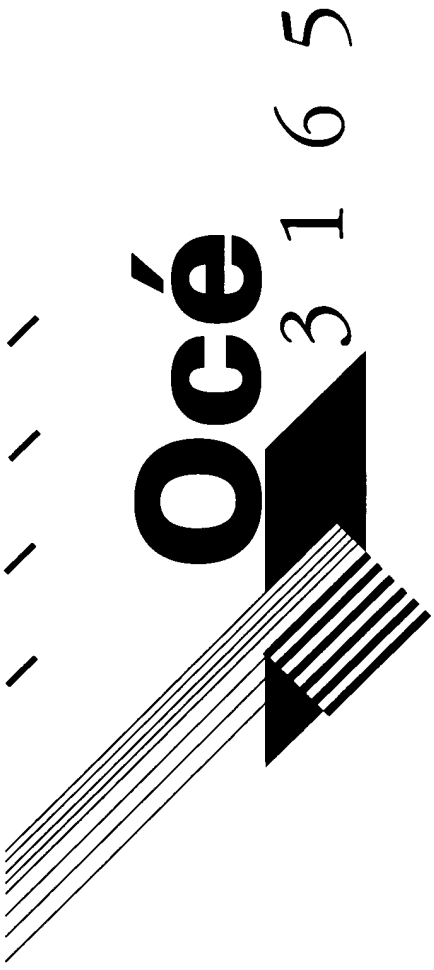


SPEED '05 Planning- IP & Legal

April 30, 2004

Feasibility FTO/LOE Grading (H/M/L) - Integration into SPEED '05

- *Selection of product Enhancement Entities*
- *Proposed by teams*
- *Decided by GDRC*

- *Attorneys provide recommendations based on a preliminary FTO assessment*
- *IP Strategic Management facilitates the process*

- *Rigorous analysis of*
- *SPEED entities by teams*

- *Attorneys provide overall IP recommendations based on thorough search and analysis.*
- *IP Strategic Management participates and ensures IP assessment in the context of the IP lifecycle plan*
- ***JULY 23: Team attorney submits to Doherty and Benson final IP assessment and H/M/L Overall IP grade .***

- *SPEED GR review of entities*
- *SPEED GR portfolio recommendation*
- *GDRC decisions for funding*

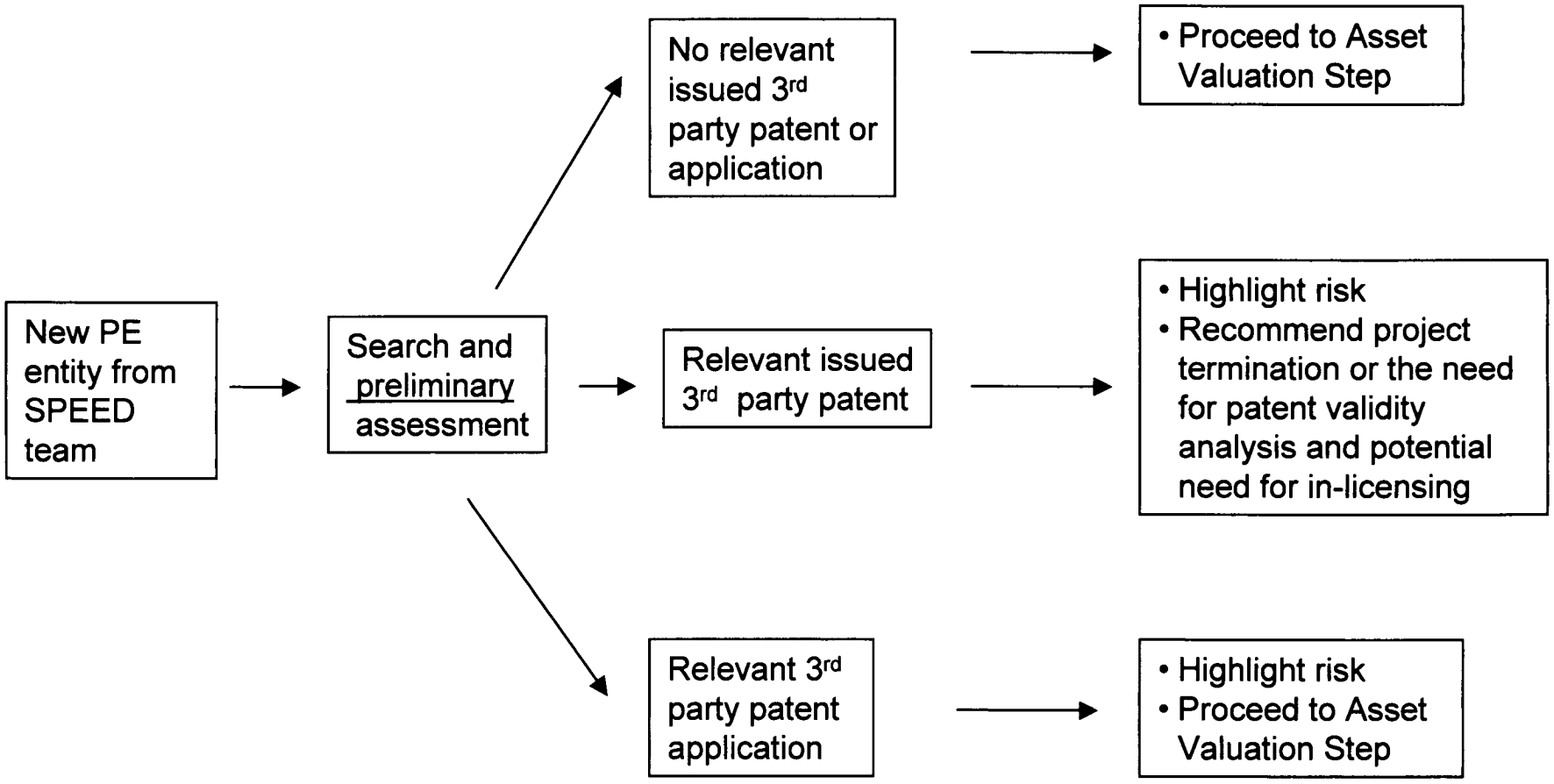
- ***Doherty and Benson perform offline consistency review H/M/L feasibility FTO/LOE for GR meeting week of August 23.***
- *Attorneys provide recommendations for decision-making*
- *IP Strategic Support & Attorneys ensure identification of action plans and follow-up*

Step 1: Entity Selection

- **Prior to entering SPEED'05, teams are informed of their eligibility for SPEED.**
- **SPEED-eligible, teams will complete an Entity Selection Template that characterizes their entity for presentation to the GDRC.**
  - Using the template, teams will provide responses to questions and criteria specifically directed at ascertaining strategic fit of idea relative to an asset's life cycle management plan, scientific merit, commercial rationale, and IP implications for a given entity proposal.
- **Specific guidance on ascertaining eligibility and the entity selection template is available in the distributed Entity Selection Guide.**
- **Once the GDRC endorses SPEED analysis, relevant teams should be ready to kick off the asset valuation stage of SPEED.**

General IP Guidance for Entity Selection, Step 1

Is there a 3rd party patent or published patent application that may be relevant to the proposed option? If the answer is "Yes", then the attorney should provide specifics that the GDRC can use to make a judgment. (Note: The relevant patent attorney is responsible for communicating with the GDRC on this issue.)



General IP Guidance for Asset Valuation

Attorney Recommendations

1. Do we have freedom to operate/commercialise?

What are the recommendations based on the FTO analysis?

2. What is our patent/exclusivity position?

What is our patent and exclusivity position for the option in its major target markets?

Can competitors adversely impact our plans (work-arounds, off-label use)

Can we strengthen our exclusivity position?

Can this option have an adverse impact on the currently projected LOE for the compound or the primary indication?

Identify IP that must be captured in Pfizer patent filings regardless of SPEED'05 approval

3. IP specific issues?

What are the IP-related value, cost and risk factors that must be taken into account in judging the SPEED entity?

Identify any unique IP-related resource issues

General IP Guidance for Asset Valuation (con't)

4. Attorney provision of Overall IP Grading

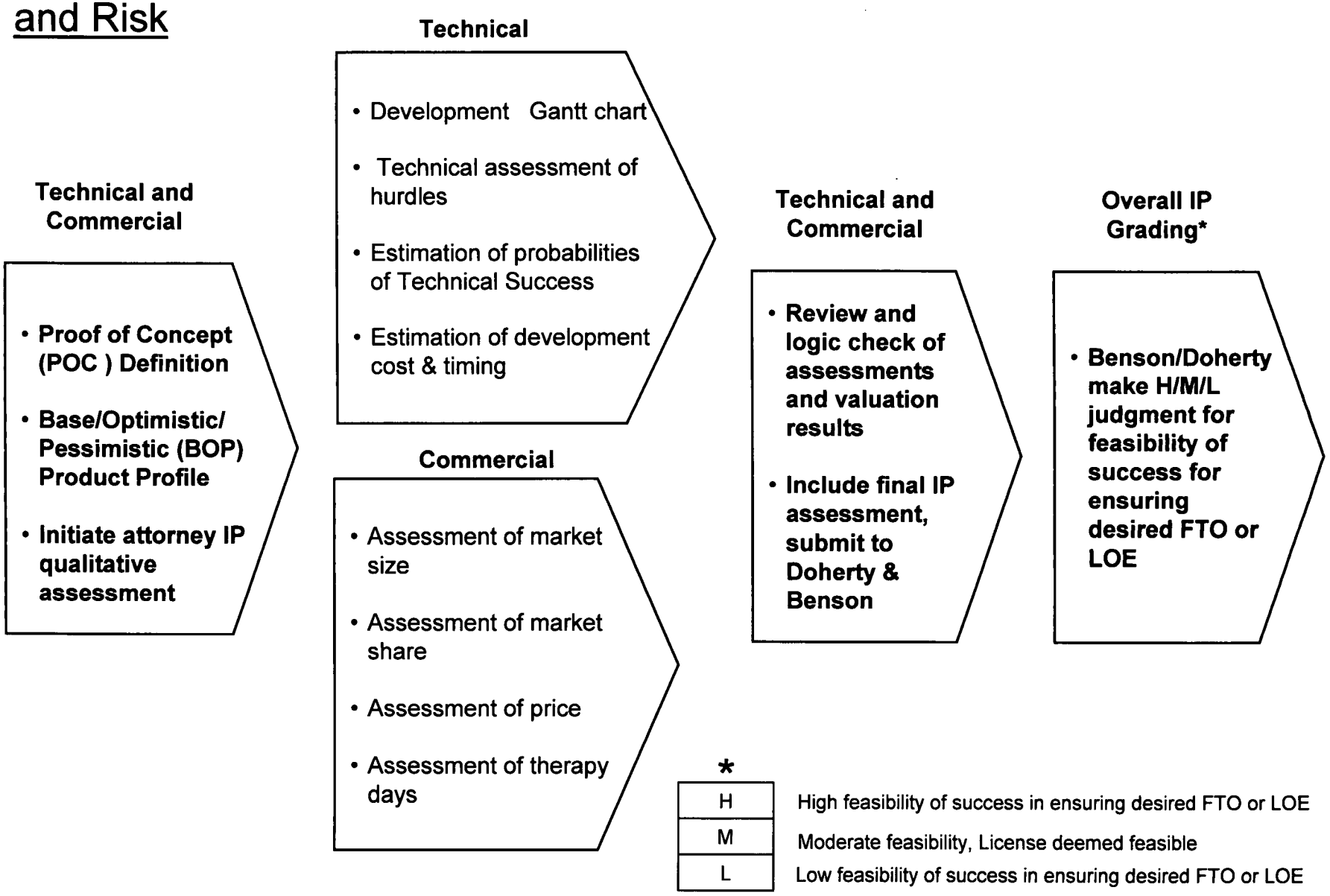
Given the team's/attorney's current assessment for IP, to what extent will proposed or current IP result in desired LOE and/or FTO? Please provide as a high, medium, or low grade for FTO feasibility, for LOE feasibility, and for combined overall IP feasibility, as illustrated in the following examples:

	FTO	+ LOE	= Overall IP	Rationale for rankings
Celebrex chewable	M	H	M	FTO: unknown formulation; LOE based on Celebrex
Relpax Migraine prophylaxis	H	H	H	LOE based on Relpax alone

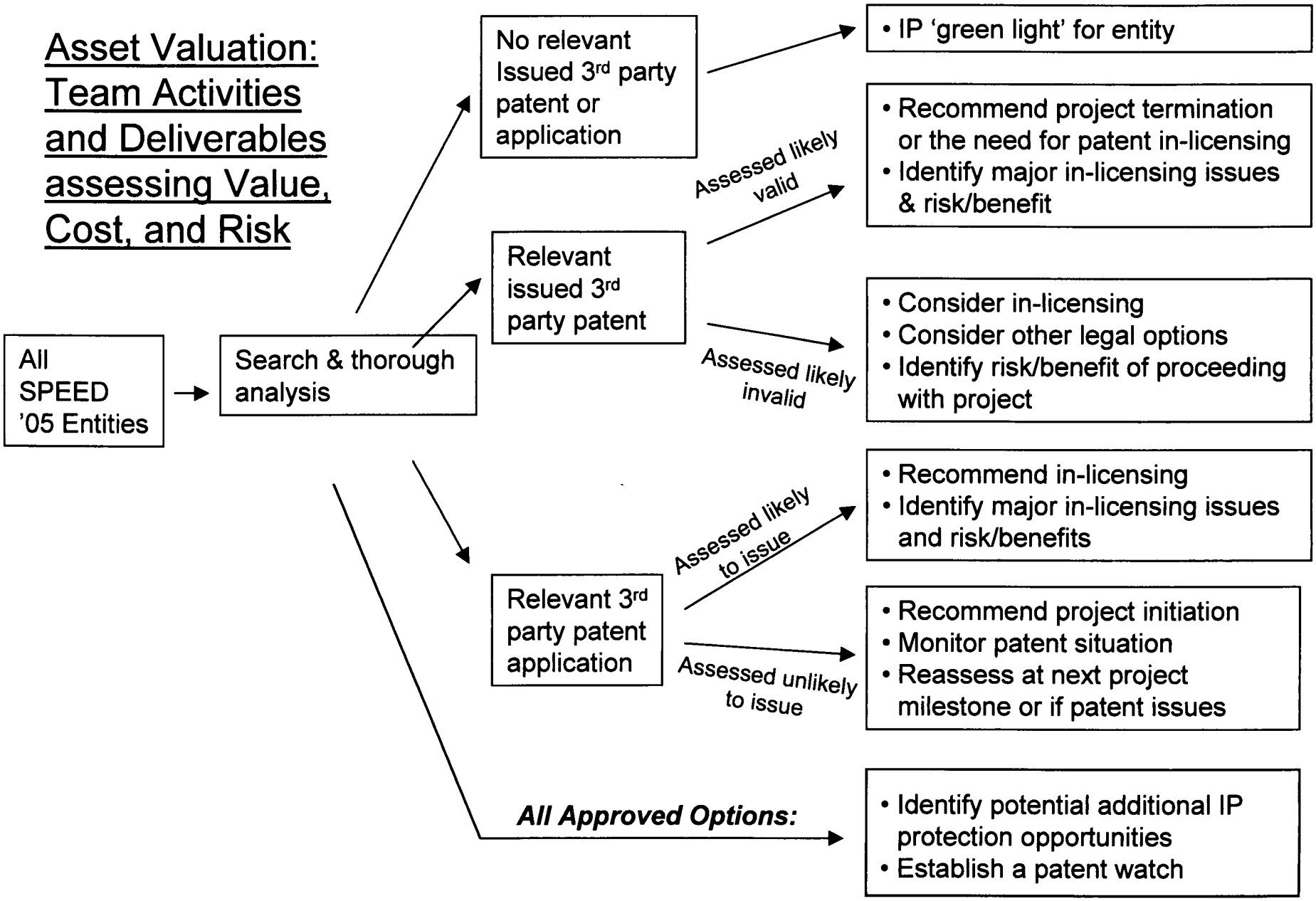
Definitions for High, Medium, Low Grades

	Rationale for FTO or LOE
H	High feasibility of success in ensuring desired FTO or LOE
M	Moderate feasibility of success in ensuring desired FTO or LOE.
L	Low feasibility of success in ensuring desired FTO or LOE

Asset Valuation: Team Activities and Deliverables assessing Value, Cost, and Risk



Asset Valuation: Team Activities and Deliverables assessing Value, Cost, and Risk



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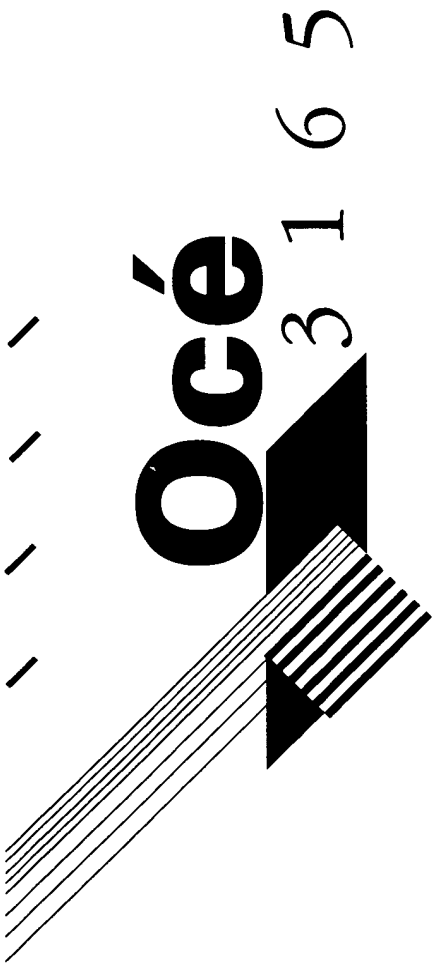

5/3/2004 first contact				
SPEED'05 Team List	**Attorney**	**IPSM**	**Location**	**GLIST member**
fragmin	Andrew Leon	Tim Lamp	AA	GR
lipitor	Frank Tinney	Sheri Hays	AA	GR
lyrica	Karen DeBenedictis	Paul Misiak	AA	GR
zyvox	Lucy Yang	Paul Misiak	AA	GR
xalatan	Joe Reidy	Bernie Greenspan	LJ	FG
celebrex combo with aromasin [breast cancer] aromasin itself is not eligible for SPEED'05	Krishna Banerjee	Dina Tresnan	NY	DKW
varenicline	David Joran	Lal Weerasinghe	NY	DKW
zeldox/geodon	Kristina Konstas	Lal Weerasinghe	NY	DKW
caduet	Dean Olson	Niall Doherty	NY/GR	BB
exubera	Jim Jones	Dina Tresnan	NY/GR	BB
torcetratib/atorvastatin	Dean Olson	Niall Doherty	NY/GR	BB
genotropin	Christine Vanhee-Brossollet	Bernard Banks	PARIS	MH
somavert	Christine Vanhee-Brossollet	Bernard Banks	PARIS	MH
bextra	Mike Warner	Jonathan Rowe	STL	JG
celebrex	Mike Warner	Jonathan Rowe	STL	JG
dynastat	Mike Warner	Jonathan Rowe	STL	JG
inspra	Scott Williams (US)	Sheri Hays	STL	JG
detrol	James Hayles	Lal Weerasinghe	SW	RP
vfend	Graham Lane	Bernard Banks	SW	RP
viagra	Watson McMunn	George Swayne	SW	RP